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ApoB IN CLINICAL CARE

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Foreword

This book was written for doctors who want to move forward, who want to give better care to their patients, and who are willing to learn how to do that. Accurate diagnosis is a core principle of clinical medicine but if only the conventional plasma and lipoprotein lipids are measured, accurate diagnosis of the atherogenic disorders of lipoprotein metabolism is not possible. Everything is reduced to one of three diagnoses: hypercholesterolemia, hypertriglyceridemia or mixed hypercholesterolemia and hypertriglyceridemia.

However, with measurement of total cholesterol, triglyceride and apoB and application of the apoB algorithm, with the exception of Lp(a), which requires a specific assay, accurate diagnosis of the apoB dyslipoproteinemias is now simple and fast.

Accurate diagnosis is the indispensable key to effective therapy for the individual patient and, as we demonstrate in this book, this principle certainly holds for the dyslipoproteinemias. Adding apoB to total cholesterol and triglyceride moves us from lipids to lipoprotein particles, from dyslipidemias to dyslipoproteinemias, from guessing what may be wrong to knowing what is wrong, from guessing what treatment should be best, to knowing which treatment is best, from just mindlessly following rules that others make, to understanding what to do and why you should do it.

With the apoB app, which is available for free in both the Apple App Store and Google Play Store, diagnosis takes only seconds and core material is immediately available. In this book, we integrate the relevant physiology, epidemiology and clinical trial results so that you can have a real understanding of how this new diagnostic and therapeutic approach works.

Cardiovascular disease is the commonest cause of death worldwide. Effective therapies are available but they need to be given to those who need them when the problem is recognized not after the complication has occurred.

This task has not been easy. Nothing worthwhile is. But without all the assistance we have received, we would not have come this far. Accordingly, we wish to thank all our colleagues who have encouraged us as well as our critics who have stimulated us. But,

most of all, we want to record our infinite thanks and love for those who have believed in us and what we are trying to do, those who have supported us and loved us in all our moments of darkness, moments that seemed to stretch into eternity. They are the light that has kept us going.

This effort is imperfect. We acknowledge that. But we believe it is a step forward and forward is where we need to go if we are to improve the outcomes of our patients.

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List of abbreviations

ACAT	Acyl-CoA Cholesterol Acyltransferase
ALP	Atherogenic Lipoprotein Phenotype
apo	apolipoprotein
ASP	Acylation Stimulating Protein
ATPII	Adult Treatment Panel II
ARH	Autosomal Recessive Hypercholesterolemia
CAD	Coronary Artery Disease
CAPD	Continuous Ambulatory Peritoneal Dialysis
CETP	Cholesterol Ester Transfer Protein
CHD	Coronary Heart Disease
CR	Chylomicron Remnants
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular Disease
DM2	Type 2 Diabetes Mellitus
ERFC	Emerging Risk Factors Collaboration
ESRD	End-Stage Renal Disease
FA	Fatty Acids
FDB	Familial Defective ApoB100
FH	Familial Hypercholesterolemia
FCH	Familial Combined Hyperlipidemia
FDBL	Familial Dysbetalipoproteinemia
FHTG	Familial Hypertriglyceridemia
GPI	Glycophosphatidylinositol
HAART	Highly Active Antiretroviral Therapy
HDL-C	High Density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HIV	Human Immunodeficiency Virus
HoFH	Homozygous Familial Hypercholesterolemia
HPS	Heart Protection Study

HR	Hazard Ratio
HSP	Hormone Sensitive Lipase
IDL	Intermediate Density Lipoprotein
JBS	Joint British Societies
LCAT	Lecithin-Cholesterol Acyltransferase
LDL-C	Low Density Lipoprotein Cholesterol
LDL-P	Low Density Lipoprotein particle number
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein Lipase
LRP	LDL-Receptor Related Protein
MTP	Microsomal Triglyceride Transfer Protein
NHANES	National Health and Nutrition Examination Survey
PCOS	Polycystic Ovary Syndrome
PCSK9	Proprotein Convertase Subtilisin Kexin Type 9
PUFA	Polyunsaturated Fatty Acids
RCT	Randomized Clinical Trial
RER	Rough endoplasmic reticulum
SER	Smooth endoplasmic reticulum
SLE	Systemic Lupus Erythematosus
SREBP	Sterol Regulatory Element Binding Protein
TC	Total Cholesterol
TG	Triglycerides
TSH	Thyroid-Stimulating Hormone
USF1	Upstream Stimulatory Factor 1
VLDL	Very Low Density Lipoprotein

Conversion of mmol/l to mg/dl

Cholesterol and triglyceride concentrations in mmol/l are converted to mg/dl by multiplying by 38.5 and 88.5, respectively.

1. The Life History of ApoB Lipoprotein Particles

1.1 Physiology of the ApoB Lipoprotein Particles

There are two families of apoB lipoprotein particles: the apoB48 lipoprotein particles and the apoB100 lipoprotein particles.

ApoB48 lipoprotein particles

The family of the apoB48 lipoprotein particles consists of chylomicrons and chylomicron remnants. Chylomicron particles are secreted by the intestine and each contains one molecule of apoB48. Initially, chylomicron particles transport dietary triglyceride to adipose tissue and muscle. Chylomicron remnants are the normal particles produced by removal of triglyceride by peripheral tissues from intact chylomicron particles and these normal remnant particles rapidly transport the residual triglyceride and all the dietary cholesterol to the liver.

Chylomicron particles are too large to penetrate the arterial wall and very few are ever present in plasma at any given time. Accordingly, they do not increase the risk of vascular disease. However, if present in large excess, they do increase the risk of pancreatitis.

By contrast, when their removal is markedly delayed in remnant lipoprotein disorder, the abnormal cholesterol-enriched chylomicron remnant particles that accumulate in large numbers increase atherogenic risk dramatically.

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ApoB100 lipoprotein particles

The family of the apoB100 lipoprotein particles consists of VLDL, IDL, LDL and Lp(a) particles. VLDL and Lp(a) particles are secreted by the liver and each contains one molecule of apoB100. VLDL particles are converted into IDL particles, which are converted into LDL particles. With only a few exceptions, there are 9 times more LDL particles than VLDL particles and they are much smaller than VLDL particles and so they can penetrate the arterial wall much more easily. That is why LDL particles are so much more important in atherogenesis than VLDL particles. Similarly, there are almost always far more VLDL particles (10-fold more) than normal chylomicron or normal chylomicron remnant particles. LDL particles, IDL particles, Lp(a) particles and abnormal VLDL remnant particles are undoubtedly atherogenic whereas whether normal VLDL particles are highly atherogenic remains controversial.

1.1.1 Introduction

There are two families of apoB lipoprotein particles: the apoB48 lipoprotein particles and the apoB100 lipoprotein particles.[1-5] ApoB48 and apoB100 are proteins, which encircle the surface of a lipoprotein particle and provide the structural framework around which it is constructed. ApoB48 is a truncated version of apoB100[6] and, in humans, one molecule of apoB48 is present on every lipoprotein particle synthesized by the intestine whereas one molecule of the full-length protein, apoB100, is present on every lipoprotein particle synthesized and secreted by the liver. The principal members of the two families of apoB lipoprotein particles are illustrated in *Figure* 1.1.

The apoB48 lipoprotein particle family consists of chylomicrons and chylomicron remnants (CR). Chylomicrons are secreted by intestinal cells following a meal and transport the dietary lipids to target tissues within the body. Chylomicron particles are too large to penetrate the arterial wall with any facility and so accumulation of chylomicrons does not increase the risk of vascular disease. However, large numbers of intact chylomicron particles do increase the risk of pancreatitis. CR are chylomicron particles from which most of the triglyceride has been removed by adipose tissue and muscle but which still contain almost all the cholesterol. CR are normal particles present in small numbers in plasma, even in the postprandial period, because they are so rapidly removed by the liver.

In remnant lipoprotein disorder, the removal of the normal CR particles is markedly delayed. Accordingly, large numbers of CR particles accumulate in plasma – 10 to 20 fold more than normal – and with their prolonged half-life in plasma, these become enriched in cholesterol. Unquestionably, atherogenic risk is markedly increased in this disorder and rapid, accurate diagnosis is one of the major practical advantages

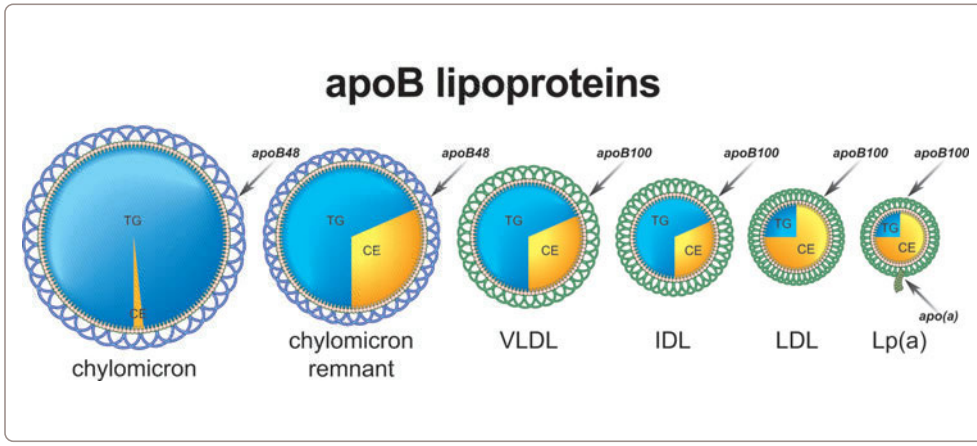

FIGURE 1.1

of the apoB algorithm. Whether atherogenic risk is significantly increased when CR removal is only slightly delayed and the number of remnant particles is only slightly increased remains controversial. In these situations, there are, on average, 10 times more very low-density lipoprotein (VLDL) particles than CR particles and generally 9 times more low-density (LDL) particles than VLDL particles.

The family of the apoB100 lipoprotein particles consists of VLDL, intermediate-density lipoprotein (IDL), LDL and Lp(a) particles. Each contains one molecule of apoB100. As will become obvious, apoB100 lipoprotein particles are much more important in atherogenesis than apoB48 lipoprotein particles because the number of apoB100 particles, almost always, is overwhelmingly greater than the number of apoB48 particles. For example, as just noted above, at the peak of the postprandial period, even in patients who are hypertriglyceridemic, with the prominent exception of those with remnant lipoprotein disorder, there are approximately 5 to 10 times more VLDL apoB100 particles than apoB48 particles. Accordingly, for convenience and in accord with usual practice, we will use apoB and apoB100 interchangeably since virtually all the apoB particles present in plasma, with the prominent but unusual exception of remnant lipoprotein disorder, are apoB100 lipoprotein particles.

1.1.2 Anatomy of the ApoB48 and ApoB100 Lipoprotein Particles

The major structural features of the apoB48 and the apoB100 lipoprotein particles are illustrated in *Figure* 1.1. Each particle has a coat and a core. Most of the lipids within the particle – cholesterol ester and triglyceride – are present within the core and the differences in size of the particles are due to differences in the mass of core lipids. The relative proportion of the core lipids differs and these differences are also characteristic of the different apoB lipoprotein particles.

For the chylomicrons and CR particles, the coat consists of a phospholipid monolayer into which an apoB48 molecule is intercalated, whereas for VLDL, IDL and LDL particles, the coat consists of a phospholipid monolayer into which one apoB100 molecule is intercalated. ApoB48 and apoB100 wrap around the outer phospholipid monolayer of the lipoprotein particles in which they are found and by doing so provide a structural backbone for the particle. Because there is only one apoB48 molecule per particle, the number of chylomicrons and CR is equal to the plasma concentration of apoB48. Similarly, the sum of VLDL, IDL, LDL, and Lp(a) – an LDL particle to which a molecule of apo(a) has been attached – is equal to the plasma apoB100.

Because apoB100 and apoB48 are critical to the architectural structure of the particle, in contrast to the many other apolipoproteins that may be present, or to the core lipids, they are fixed constituents of the particle during its entire lifetime. Free cholesterol has a limited solubility in phospholipid membranes and that is where it is found in the coat of the lipoprotein particles. By contrast, cholesterol ester – that is, cholesterol to which a fatty acid has been joined – is virtually insoluble and immiscible in water and accordingly is found within the core of the particle. This also applies to triglyceride, which is also insoluble and immiscible in water.

Although apoB48 and apoB100 are the signature apolipoproteins, a series of other apolipoproteins including apoE, apoCI, apoCII, apoCIII, apoAI, apoAIV, apoAV are scattered on the surface of chylomicrons and VLDL. Some of these are present when the particle is secreted from its site of synthesis while others are transferred from other lipoprotein particles during their lifetimes in plasma. Many influence critical steps in the metabolism of the lipoprotein particles whereas the function(s) of others remains unknown. In contrast to apoB48 and apoB100, these apolipoproteins are not fixed constituents of the particles but attach and detach relatively freely during their lifetime.

Much remains to be learned about the function of these apolipoproteins. ApoCIII, in particular, seems to be an important determinant of VLDL metabolism and there is considerable evidence linking increased apoCIII to increased cardiovascular risk.[7,8] It remains uncertain, however, whether this association is independent of any effect of apoCIII on VLDL or LDL particle number. Even if it were not, as is not unlikely, that would not diminish the significance of apoCIII as a potential therapeutic tool to manipulate VLDL or LDL particle number.

The major components of apoB48 and apoB100 particles are summarized in *Table* 1.[9]

Table 1.1 Major Components of ApoB48 and ApoB100 Particles

	Chylomicron	VLDL	IDL	LDL
Density (g/ml)	~ 0.93	0.93-1.006	1.006-1.019	1.019-1.063
Diameter (nm)	75-1200	30-80	25-35	18-25
Surface components				
Total Apolipoprotein content	1-2%	8%	19%	22%
ApoB48	+	-	-	-
ApoB100	-	+	+	+
ApoCI	+	+	+	-
ApoCII	+	+	+	-
ApoCIII	+	+	+	-
ApoE	+	+	+	-
ApoAI	+	+	-	-
ApoAIV	+	+	-	-
ApoAV	+	+	-	-
Surface Lipids				
Cholesterol	1-3%	7%	9%	8%
Phospholipids	7-9%	18%	19%	22%
Core Lipids				
Triglycerides	85-90%	55%	23%	6%
Cholesterol Esters	1 - 3%	12%	29%	42%

1.1.3 The ApoB48 Lipoprotein Particles: Chylomicrons and Chylomicron Remnants

Physiological Role

The triglyceride and cholesterol within the food we eat are absorbed by the microvillar cells of the intestine, within which they are assembled into nascent chylomicron particles, which are secreted into the lymph and then into plasma, and within which they are delivered via the circulation to selected sites within our bodies. The amount of each of these major lipids that we ingest per day varies and is determined by the wealth of the society in which we live, our individual wealth within that society, and the dietary culture of our society. The mass of triglycerides always far exceeds the mass of cholesterol. On average, in affluent Western cultures, we ingest about 100 g of triglycerides versus 500 mg or less cholesterol per day. Triglycerides provide us with fatty acids and fatty acids are one of our principal sources of energy (*Figure 1.2*).