# Biomarkers for Cholesterol Absorption and Synthesis in Hyperlipidemic Patients

## Role for Therapeutic Selection

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**KEYWORDS**

• Statins • Ezetimibe • Campesterol • Lathosterol • β-Sitosterol • Squalene
• Desmosterol • Cholestanol

**KEY POINTS**

- Hypercholesterolemia is caused by increased rate of synthesis or absorption from the diet.
- Biomarkers of increased synthesis include squalene, desmosterol, and lathosterol.
- Biomarkers of increased absorption include campesterol, β-sitosterol, and cholestanol.
- Statins are most effective when used in patients with increased synthesis.
- Cholesterol absorption drugs, such as ezetimibe, are most effective in patients with increased absorption.

### INTRODUCTION

Increased total serum cholesterol and low-density lipoprotein (LDL) cholesterol concentrations are associated with atherosclerosis and risk for myocardial infarction and stroke. International guidelines, such as from the National Cholesterol Education Program, have established cutoff concentrations for total and LDL cholesterol that identify individuals at moderate and high risk for future adverse cardiac events.[1] Individuals with a borderline cholesterol concentration with few or no other risk factors are at moderate risk and should undergo modifications in their diet, exercise, and smoking habits. Those who have high cholesterol with other factors that predisposes them to cardiovascular disease are at the highest risk should be treated with cholesterol-lowering medications. The pathophysiology of hyperlipidemia is important in the proper selection of drug therapy. Patients who have increased cholesterol synthesis should be medicated with drugs that reduce *in vivo* cholesterol production, whereas

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those who have increased dietary absorption of cholesterol should be treated with drugs that inhibit dietary absorption. Sterol-based biomarkers are available to assess the cause of hypercholesterolemia and may have an impact on therapeutic selection.

## BIOMARKERS OF CHOLESTEROL SYNTHESIS AND ABSORPTION

### *Cholesterol Synthesis Pathway*

Cholesterol produced in mammalian cells originates from acetate. The important steps are shown in **Fig. 1**.[2] Acetate is converted to 3-hydroxy-3-methyl-glutaryl-CoA (HMG) by HMG-CoA synthase and then to mevalonate by HMG-CoA reductase. The class of statin drugs reduces cholesterol synthesis by inhibiting this important rate-limiting step. In the absence of statins, mevalonate is converted to squalene and then to lanosterol. Subsequently, there are two different pathways that convert lanosterol to cholesterol. In the Bloch pathway, lanosterol is converted to desmosterol. In the Kandutsch-Russell pathway, lanosterol is first converted to lathosterol, then 7-dehydrocholesterol, and finally cholesterol. The intermediate metabolites squalene, lathosterol, and desmosterol are used as biomarkers to evaluate cholesterol synthesis. High concentrations of these markers indicate increased in vivo production. The value of measuring cholesterol precursors depends on the presumption that the serum or plasma concentrations of these biomarkers are proportional to their formation in the synthetic pathway. Bjorkhem and colleagues[3] showed that there was a linear relationship between absolute total serum lathosterol concentration and hepatic HMG-CoA reductase activity ($r$ =0.82). In this study, the correlation of enzyme activity to desmosterol and squalene was weaker ($r$ = 0.50 and 0.20, respectively).

### *Mechanism of Cholesterol Absorption*

The manner by which cholesterol is absorbed from lumen has been studied extensively. According to Wang,[4] intestinal cholesterol originates from dietary absorption, the bile, and intestinal epithelial slothing. Collectively, these sources contribute roughly 2000 mg/day. A western diet contributes about 300 to 500 mg of this total by absorption through the duodenum and proximal jejunum. The cholesterol forms micelles in conjunction with bile salts, phospholipids, and monoglycerides. Micelles formation facilitates transport of cholesterol to the brush border of the small intestines. There, cholesterol is removed from the micelles and monomeric unesterified cholesterol is passed through to enterocytes through the Niemann-Pick C1-like (NPC1) transporter. Once absorbed, cholesterol is esterified by CoA:cholesterol acyltransferase. Efflux from the enterocyte seems to be mediated by intestinal ATP-binding cassette transporters (ABC) G5 and G8 proteins. There are genetic variances of this protein that results in the hyperabsorption of cholesterol.[5]

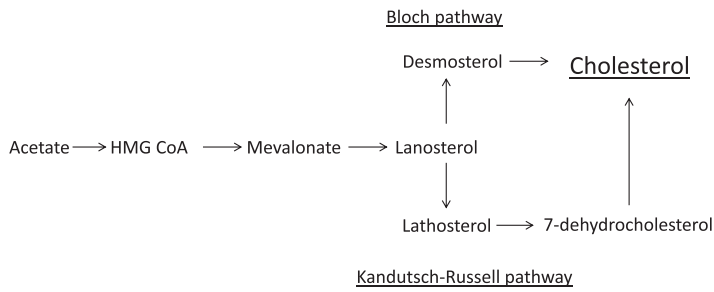


**Fig. 1.** Cholesterol synthesis pathways.