EDITORIAL REVIEW

Nutrition and therapeutics: where we are and where we should be going

Henry N. Ginsberg and Martijn B. Katan*

Department of Medicine, College of Physicians and Surgeons of Columbia University, New York, USA, and *Department of Human Nutrition, Wageningen Agricultural University, Wageningen, The Netherlands

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In this issue several experts provide reviews of the recent progress in the fields of nutrition and therapeutics as it relates to lipids, lipoproteins, and cardiovascular disease. We have clearly come a long way in understanding the regulation of lipid and lipoprotein metabolism in humans. The impact of various drugs and dietary factors and our ability to use pharmacologic agents to modify inherited dyslipidemia has increased dramatically in the past 20 years. However, controversies, knowledge gaps, and suboptimal choices still remain. We will discuss several of these in detail.

Scientists involved in human nutrition studies must resolve a number of major issues. Our basic understanding of how dietary fatty acids affect plasma LDL concentrations has benefitted greatly from the studies of Spady et al. [1] in hamsters that have pinpointed the esterification of liver cholesterol by the acyl-coenzyme A: cholesterol acyltransferase enzyme as a key step. However, it is still uncertain to what extent this mechanism operates in humans. An investigation of the role of this pathway in humans is eagerly awaited but will not be easy.

The cholesterol-raising effects of individual fatty acids also need to be dealt with in a definitive manner. Despite the landmark studies by Keys et al. [2] and Hegsted et al. [3] and the more recent work by Bonanome and Grundy [4], Nestel et al. [5], and Zock et al. [6], the proper assignment of stearic acid remains unclear, especially as regards its effects on HDL. The potency of palmitic acid as a cholesterol-raising fatty acid is also doubted by some investigators. What are the health effects of dietary trans-fatty acids and why is there still uncertainty? One problem derives from the almost infinite number of study designs and protocols that have been used to address similar questions. No two protocols studied the same population, had the same degree of dietary control, or used the same 'control' diet. Thus, critics or special interest groups can always criticize the results. Larger, multicenter diet studies, which maintained the same levels of control achieved in the small metabolic studies, have the potential to resolve some of the controversies, but the cost and effort involved are great.

Another major question is whether low-fat diets (higher in carbohydrates) or high-unsaturated-fat diets (higher in monounsaturated or polyunsaturated fats) are best for many individuals at risk of developing atherosclerotic cardiovascular disease. Low-fat diets reduce LDL-cholesterol levels and may reduce body weight, although direct evidence from long-term trials is surprisingly tenuous. However, low-fat diets also reduce HDL levels and raise VLDL and triglyceride levels. The classical low-fat, low-saturated-fat diet is clearly efficacious in individuals with high total and LDL cholesterol as their sole lipid problem. The efficacy of such diets is much less clear in individuals with normal or slightly elevated total cholesterol, increased triglyceride levels, and low levels of HDL cholesterol. These individuals also have an increased coprevalence of noninsulin-dependent diabetes mellitus and would, according to Garg et al. [7], benefit from reducing dietary carbohydrate and substituting monounsaturated fat for saturated fat. The solution for the problem is confounded by the potential effects of higher-fat, more calorie-dense diets on weight gain and postprandial lipoprotein remnants. Again, long-term, carefully controlled trials with angiographic or clinical endpoints are the only hope for resolving this controversy.

The first large clinical trial of dietary antioxidants, the Finnish Alpha-Tocopherol Beta-Carotene Trial [8], failed to find any benefit of beta-carotene or vitamin E and raised the spectre of a beautiful theory slain by an ugly fact. More trials are in the pipeline and their results are awaited eagerly.

Pharmacologic therapy of dyslipidemia is not so much mired in controversy as it is stymied by the inability of researchers to develop agents that are effective at both lowering LDL cholesterol and raising HDL cholesterol. The past 10 years has seen major advances in pharmacotherapy with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors leading the parade. The 'statins' have revolutionized the treatment of hypercholesterolemia, providing physicians with a simple, easy-to-take medication that can cause significant reductions in total and LDL-cholesterol levels. The reduced use by physicians of the safe and effective bile acid sequestrants is a downside, but is far outweighed by the positive effect of removing the major stumbling block to physician intervention for cases of elevated LDL cholesterol. The availability of
potent reductase inhibitors has also enabled investigators
to dramatically reduce LDL levels in clinical trials. Re-
cent studies, such as the Asymptomatic Carotid Artery
Plaque Study, the Pravastatin Limitation of Atheroscle-
rosis in Coronary Arteries Protocol 1, and the Pravas-
tatin, Lipids and Atherosclerosis in the Carotid Arteries
Protocol 2, have confirmed and extended the results of
earlier trials in which less potent agents were used alone
[9] or in combination [10,11]. The availability of safe,
potent, cholesterol-lowering agents has also made aggre-
gressive secondary prevention possible. Clinical results
of long-term treatment with simvastatin have recently
become available [12]. Both coronary and total mor-
tality were reduced markedly, whereas noncardiovascular
events were unaffected.

All of this good news is balanced by our inability to
modify plasma lipid levels optimally in many, if not
the majority, of patients at very high risks of de-
veloping coronary disease. These patients with elevated
triglyceride levels, reduced levels of HDL cholesterol,
and normal or slightly elevated levels of LDL choles-
terol have a pathophysiologic state that is quite distinct
from patients with only elevated LDL-cholesterol levels.
The fibrates and niacin are the only available therapies
for these individuals and both are effective at reducing
triglyceride concentrations and raising HDL-cholesterol
levels. Niacin has the additional ability of lowering LDL
cholesterol. In the Coronary Drug Project trial, niacin
reduced nonfatal myocardial infarctions and the long-
term follow up of trial participants indicated that niacin
was associated with decreased total mortality [13]. Gem-
fibrozil reduced cardiovascular events by more than 30%
in the Helsinki Heart Study [14]. However, both of
these agents have significant shortcomings. The fibrates
have been associated with increased gastrointestinal
disease, particularly gallstones, in several large trials. Niacin
has many troublesome side effects, such as flushing and
swelling, and can cause significant hepatic dysfunction.
In addition, the effectiveness of both fibrates and niacin
in raising HDL cholesterol is limited in individuals with
low HDL levels but relatively normal triglyceride levels.

What is needed is a drug that reduces triglyceride
levels, raises HDL, and lowers LDL. Ideally a safe agent
that reduces the formation and secretion of apolipoprotein B-
containing lipoproteins from the liver would accomplish
these goals. VLDL and LDL levels would fall and HDL
cholesterol would rise via the reduced cholesteryl ester
transfer protein mediated exchange of HDL cholesteryl
ester for VLDL triglyceride (the major stimulus to that
exchange). Recent findings related to the regulation of
apolipoprotein B secretion, including the identification of
microsomal triglyceride transfer protein, offer hope in
this area. Another major effort should be focused on the
development of agents that raise apolipoprotein A-I syn-
thesis in the liver or the intestine. Studies from transgenic
mice indicate that such a strategy might be a potent way
to inhibit atherosclerosis in individuals with other lipid
abnormalities.

Diet therapy remains the initial approach to the high-
risk, dyslipidemic patient. Progress has been made but
important points remain to be negotiated. Drug treat-
ment of elevated LDL-cholesterol levels has been simpli-
fied by the availability of statins. Now we must tackle
the very common and more complex problems of de-
rangements in triglyceride and HDL metabolism.

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Martijn B. Katan, Department of Human Nutrition, Wageningen
Agricultural University, Bomenweg 2, 6703 HD Wageningen, The
Netherlands.