Review Article

The Role of Bile Acid Excretion in Atherosclerotic Coronary Artery Disease

Gideon Charach, Alexander Rabinovich, Ori Argov, Moshe Weintraub, and Pavel Rabinovich

Department of Internal Medicine “C”, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel

Correspondence should be addressed to Gideon Charach, drcharach@012.net.il

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The impact of cholesterol and different classes of lipoproteins on the development of coronary artery disease (CAD) has been investigated extensively during the past 50 years. The cholesterol metabolism is dependent on numerous factors, including dietary fat, fractional absorption of dietary cholesterol, tissue stores of cholesterol, endogenous cholesterol synthesis, and fecal bile excretion. Several studies showed significantly lower amounts of bile acid secretion in adult patients with CAD compared to non-CAD patients. Could it be that the inability to efficiently excrete bile acids may lead to CAD development?

1. Introduction

While a great deal of attention has been given to the factors that determine cholesterol homeostasis, cholesterol excretion via bile in patients with CAD has not been thoroughly examined [1–3].

Clinically, it became obvious that, despite effective cholesterol-modulating treatment (e.g., statins), the development of atherosclerosis cannot be stopped in a significant number of patients. It is known that cholesterol is mainly eliminated from the body via the liver in the form of bile acids [2, 4, 5]. Therefore, in addition to statins, low-density lipoprotein cholesterol (LDL-c) can be reduced by increasing the fecal bile acid waste and by compensatory hepatic upregulation of bile acid synthesis [2, 4].

It is reasonable to speculate that a reduced ability to convert cholesterol to bile acids would lead to body cholesterol overload, with the subsequent development of atherosclerosis [6–10]. The aim of this paper is to emphasize the effect of bile acid disposal on coronary artery atherosclerosis.

2. Bile Acid Excretion and Its Relationship to Coronary Atherosclerosis

2.1. Animal Studies. Studies in animals have revealed that rodents do not develop experimental atherosclerosis, despite ingestion of a cholesterol-rich diet [2, 11–13]. They were able to react to the overload of cholesterol intake by excreting large amounts of bile acids. The same results were obtained in a study on New Zealand white rabbits and primates which were also fed a cholesterol-rich diet [14]. Animals that excreted large amounts of cholesterol did not develop hypercholesterolemia, whereas those with a less efficient excretion had increased plasma level of cholesterol [14]. Furthermore, the degree of hypercholesterolemia was inversely correlated to the rate of bile acid elimination. These animal experiments suggest that the atherogenic effect of the cholesterol-rich diet closely depends on the animal’s ability to eliminate cholesterol in the form of bile acids [12, 13]. It is therefore reasonable to speculate that reduced ability to convert cholesterol to bile acids would lead to cholesterol overload, with the possibility of subsequent enhanced development of atherosclerosis [6–10]. A similar correlation between the elimination of cholesterol in bile and the development of atherosclerosis was suggested for humans.

2.2. Human Studies. In an earlier investigation the elimination of bile acid in the feces of patients who had ischemic heart disease was compared with that of healthy controls on the same diet [15]. It was reported that the patients excreted much fewer bile acids than the controls [15].
Several new studies had shown an inverse relationship between CAD and bile acid excretion [6–10, 16, 17]. There are few human studies dealing with disturbed metabolism of plant sterols (which reflects cholesterol) in postmenopausal CAD women who showed disturbed synthesis and disturbed secretion of bile acids [15, 16].

These findings support the hypothesis that CAD patients produce fewer bile acids than individuals without CAD and that reduced production of bile acids could lead to advanced atherosclerosis. These findings are in line with those of the several human studies that showed increased fecal excretion of bile acids to have protective effect on CAD development [6–10, 15–17]. Most of those investigations were done on selected populations using the method described by Grundy et al. [18] for determination of total bile acids. For example, Simonen and Miettinen [19] showed that males with heterozygous familial hypercholesterolemia (FH) and CAD excreted less bile acids than control males with FH and normal coronaries. Rajaratnam et al. showed that postmenopausal women with CAD had inefficient fecal elimination of cholesterol [17].

Atherosclerosis is a disease characterized by lipid accumulation in the vascular wall leading to myocardial infarction or stroke [20–22]. In spite of proven efficacy of the existing drugs, like statins, cardiovascular diseases still remain the most important causes of morbidity and mortality in industrialized countries. A cholesterol-lowering effect can be achieved by reducing cholesterol synthesis or by increasing fecal excretion of bile acids (ileal sodium-dependent bile acid transporter inhibitors). It is important to emphasize that the ability to excrete large amounts of bile acids not only prevents CAD development but also may also prevent atherosclerosis in the cerebral arteries as well [3, 21, 22].

The results of the recent study after a long follow-up pointed out to a 6-fold higher incidence of ischemic stroke among the CAD patients compared to the non-CAD patients, 7 patients (19%) versus 1 patient (2.7%), and threefold greater mortality in the CAD group, 9 patients (25%) versus 3 patient (8%) [3].

5. 7-α Hydroxylase: The Main Enzyme Responsible for Bile Acids Excretion

The 7-α hydroxylase is the key enzyme in the conversion of cholesterol to bile acids [12, 13, 21, 23, 24]. It mediates the elimination of cholesterol from the plasma and the intracellular compartment, and it facilitates the excretion of bile acids. Thus, enhanced excretion of bile acids in non-CAD individuals can possibly be explained mainly by increased activity and concentration of 7-α-hydroxylase [12, 13, 21, 23, 24]. In contrast to it, CAD patients are unable to effectively increase the activity and concentration of 7-α-hydroxylase [23].

6. Future Perspective: Combined Treatment with Statins and Bile Acid Sequestrants

A significant percentage of patients develop atherosclerosis despite statin treatment and suppressed levels of cholesterol. We reason that, by decreasing cholesterol synthesis and increasing the utility of cholesterol, an additive antiatherosclerosis effect might be achieved. This is particularly true in the case of patients at high risk for CAD. To date it is established that these patients require aggressive lipid-lowering therapy. By combining a statin with drugs affecting bile acid and cholesterol absorption an optimal management of dyslipidemia may potentially be ensured. Additional studies are necessary to validate our contention.

7. Conclusion

Reviewing of several human studies revealed significantly lower excretion of bile acid in adult patients with CAD compared to non-CAD individuals. The diminished excretion of bile acids might be an independent risk factor for CAD and a potential target for cholesterol lowering treatment.

References


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