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Review

Where does the interplay between cholesterol absorption and synthesis in the context of statin and/or ezetimibe treatment stand today?

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ABSTRACT

The evidence of the different concepts underlying the interplay between cholesterol absorption and synthesis in the context of statin and ezetimibe treatment were reviewed in the light of the eight major trials where cholesterol absorption and synthesis were analyzed on a large scale using the plasma levels of precursors of cholesterol and plant sterols. The only concept supported in all studies is a significant and consistent increase of cholesterol absorption with statin (correlated with the inhibition of synthesis) and of cholesterol synthesis with ezetimibe, whereas in combination, statin and ezetimibe reduce both cholesterol synthesis and absorption. In contrast, most of the other concepts failed to be clearly proven. At baseline, the inverse relationship between cholesterol absorption and synthesis (only examined in two studies) was found to be weak. On statin treatment, four studies showed that the changes in cholesterol synthesis and absorption, contributed less than 9% to the variability in cholesterol response to statin therapy. It has not been consistently demonstrated that good absorbers/bad synthesizers are bad responders to statin (6 studies) and good responders for ezetimibe (3 studies). There is also no clear inverse correlation between LDL reduction on statin treatment and that on ezetimibe treatment. Finally, the original idea from the first pioneer study of Miettinen et al. that, the higher the baseline intestinal ability to absorb cholesterol, the lower the benefit on the clinical cardiovascular outcomes was not reproduced in the PROSPER study. In conclusion, with the exception of a reverse effect of statin and ezetimibe on absorption and synthesis, most ideas supporting the interplay between cholesterol absorption and synthesis lacked consistency between studies. At present, the use of the plasma levels of plant sterols and cholesterol precursors as markers of cholesterol absorption and synthesis is far too limited to definitively solve these questions.

Contents

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1. Introduction

Although usually only the mean reduction of low density lipoprotein cholesterol (LDL-C) is reported in published papers, there is wide variation in the response of LDL-C to statins, varying from a reduction of 70% to an increase of 10% [1,2]. Besides compliance and measurement errors, many reasons have been suggested to explain this variability [3,4]. Explanations include dietary intake of cholesterol [5], baseline cholesterol [5–9] body weight [10–12], triglyceride levels [9], age, sex, alcohol intake [8], smoking [5], and race [13–16]. A further explanation is that genetic variation in more than 30 genes, including drug-metabolizing enzymes and lipoprotein metabolism genes, such as the e4 allele and apoprotein(a) may also cause variability in the response [7,17–19]. However even then, only a few percent of the variability is explained by taking these factors into account. Probably the most important determinants of the response to statins are baseline absorption and synthesis of cholesterol. Studies on the influence of cholesterol absorption and synthesis on the effect of statin treatment on cholesterol levels and cardiovascular disease (CVD) have resulted in several ideas that can logically be linked together to give a conceptual chart (Fig. 1).

1.1. Conceptual Chart of the interplay between sterol absorption and cholesterol synthesis.

Most of the ideas in Fig. 1 emerged from the early study of Miettinen at al [11,20] who measured cholesterol absorption by cholestanol/cholesterol ratio (see below). In the post-hoc analysis of the Finnish subgroup of the Scandinavian Simvastatin Survival Study (4S), coronary patients with a high rate of cholesterol absorption failed to benefit from statin therapy whereas patients with low absorption did experience a reduction in coronary events [20] (concept #5 in Fig. 1). From this observation, the authors suggested that subjects with high cholesterol absorption have lower baseline cholesterol synthesis (concept #1). In other words, cholesterol synthesis and absorption are inversely linked in maintaining a constant cholesterol balance. They suggest also, that statins are less efficient in lowering LDL-C in patients with high cholesterol absorption (concept #3).

A second paper by the same group [11] confirmed these 2 hypotheses and showed in addition, that inhibition of cholesterol synthesis by statin is associated with an increase in cholesterol absorption (concept #2). In fact, this idea appears reciprocal to the very early observation that an excess of dietary sterols results in a reduction of endogenous cholesterol synthesis [21,22] (concept #0). This idea also raises the possibility of a counteractive mechanism operating against the benefit of statin, in terms of LDL-C reduction and cardiovascular event response. On the one hand, LDL-C reduction induced by inhibition of cholesterol synthesis by statins may be slightly offset by increase in cholesterol absorption. On the other hand, the reduction of atherosclerosis expected from the statin-induced LDL-C reduction may be slightly offset by the statin-induced increase of plant sterols (PS) (PS absorption and cholesterol absorption follow the same direction [12,23], and thus both increase by statin [concept #4] [11,24]) as increase of PS levels may potentially promote atherosclerosis [25].

In this scheme, ezetimibe, a cholesterol absorption blocker (concept #2′A), may reduce (concept #6) the unfavorable compensatory increase in cholesterol absorption induced by statin (concept #2B). By inhibiting plant sterol absorption (concept #2′A), it may also reduce (concept #4′) the increased plant sterol concentration adversely induced by statins (concept #4) [26]. Furthermore, the possibility arises that ezetimibe would be more efficient in subjects with high cholesterol absorption and low synthesis (concept #3′), i.e. in patients who responded poorly to statins [26]. Therefore, it was extrapolated from concept 3 and 3′ that the LDL-C lowering effect of statin and ezetimibe would be inversely correlated (concept #7) and that ezetimibe would be more efficacious in patients with high cholesterol absorption (concept #5′) than in patients with low cholesterol synthesis and that, in attempting to achieve a specific LDL-C target, it would more efficient to add ezetimibe than to increase the dosage or power of statin, especially in patients with high cholesterol absorption (concept #8).

Fig. 1 displays all the concepts derived from a possible reciprocal interplay between absorption and synthesis at baseline and during the treatment affecting one or another. It shows the conceptual cascade by which the various concepts are linked to each other in the most logical way. It has the advantage of providing a good model to confront one by one each concept according to the evidence of current studies. With the exception of concept #5′ and 8, all concepts have been analyzed in several studies.

1.2. Plasma levels of Plant sterol and cholesterol precursors as a tool to measure sterol absorption and cholesterol synthesis.

Most of these ideas are based on the assessment of cholesterol synthesis/absorption by quantification of cholesterol precursors and plant sterols. The sterols used to measure cholesterol absorption are mainly cholestanol and PS levels, such as campesterol and sitosterol which were those most commonly used. Cholestanol is an endogenous biliary sterol (also taken up, to a small extent, from meat) and its blood concentration was shown to be very well correlated [27] with fractional cholesterol absorption measured by the fecal excretion of isotopic cholesterol and the isotopic nonabsorbed marker (sitosterol) measured by the classical method of Crouse and Grundy [28]. As they cannot be synthesized by the human body and therefore result exclusively from absorption, PS were used as more reliable markers of cholesterol absorption. In several studies, it was shown that PS concentrations are positively correlated with cholestanol concentration [11]. PS serum concentrations are only 0.3% (for campesterol: 0.0–0.7 mg/dL; mean value ≈0.4 mg/dL)