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Cholesterol Overproducers and Hyperabsorbers

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Abstract

About 15% of the general population are extreme high absorbers of cholesterol and about 2% are overproducers. This has consequences with respect to the choice of the lipid lowering treatment. High absorbers only poorly respond to statin therapy, while high synthesizers are poor responders to drugs which inhibit cholesterol absorption, such as ezetimibe. The response of LDL-C is regulated by polymorphisms of the HMG CoA Reductase, targeted by statins and the NPC1/1 genes, targeted by ezetimibe. Other important players especially in cholesterol absorption are alleles of the Apo E gene and the apolipoprotein A-IV.

Keywords: *Cholesterol; Overproducers; Hyperabsorbers*

The clinical consequences as shown in a post hoc analysis of the 4S trial [1] is that with increasing quartiles of cholesterol absorption the response to the statin treatment decreased and the ratio of coronary events increased.

The counter regulation of cholesterol synthesis and absorption by the combination of a statin with a cholesterol absorption inhibitor, like ezetimibe is expected to improve patient outcomes and minimize costs of treatment.

Around 15% of the general population are extreme "high absorbers" and 2% are extreme "overproducers" of cholesterol, i.e. the proportion of cholesterol absorption or cholesterol synthesis respectively exceeds 70% [1]. In about one third of the general population the proportion of cholesterol synthesis is more than 60%. High cholesterol absorbers almost do not respond to statin therapy, but high synthesizer do, while not responding to absorption inhibitors like ezetimibe The characteristics of high absorbers and overproducers are shown in table 1.

Characteristics	High Absorbers	Overproducers
Target organ	Intestine	Liver
Bichemical substrate	NPC1/1 protein	HMG CoA reductase
Metabolic phenotype	Insulin sensitive	Insulin resistent (obesity, T2DM)
LDL-C with statin	Weak decrease	Strong decrease
CV protection with statin	Controversial	Proven
Therapeutic adjustment	Ezetimibe	Increase of statin dose

Table 1: *Characteristics of high absorbers and overproducers of cholesterol.*

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For the detection of cholesterol synthesis, the ratio of lathosterol/cholesterol may be used. This ratio reflects the activity of HMG CoA reductase activity in the liver and the synthesis of total cholesterol [2,3]. For cholesterol absorption the ratio of cholestenaol/cholesterol is a good indicator [3,4].

Differences in response of LDL-cholesterol to statins and to ezetimibe and the influence of NPC1/1 and HMGCoA-receptor polymorphisms

The individual LDL-cholesterol response to statins or to ezetimibe may be different in various patients as has been demonstrated for rosuvastatin and atorvastatin [5]. The response of LDL-cholesterol to rosuvastatin may vary from around -80% to + 15% and for atorvastatin from -80% to 0%. The same is true for cholesterol absorption inhibitor ezetimibe where differences in the change of LDL-cholesterol between -70% and +10% may be observed [6].

The Niemann-Pick C1-Like 1 (NPC1/1) is a sterol transporter of the Niemann Pick family protein, whose main task is the absorption or resorption of cholesterol and other lipids from the intestinal lumen into the cells. Inactivating mutations lead to lower cholesterol levels. Ezetimibe blocks NPC1/1 and thus causes a reduction in cholesterol absorption, which leads to a decrease in plasma cholesterol of about 15 - 20%. There is no difference in LDL-cholesterol lowering by inhibition of NPC1/1 or HMGCoA reductase on the cardiovascular risk as has been shown by the comparison of the effect of a 10mg/dl lower LDL-C level on the CHD risk by polymorphisms in the NPC1/1 and HNGCoA reductase genetic scores [7]. The combination of both polymorphism of NPC1/1 and HMGCoA reductase is associated with a linear additive effect on plasma LDL cholesterol and with a log linear effect on the cardiovascular risk [7]. The fact that the decrease of LDL cholesterol no matter of its lowering method leads to the same reduction of the cardiovascular risk, as has been shown in the IMPROVE-IT study with simvastatin and ezetimibe vs. simvastatin alone [8]. The IMPROVE-IT data perfectly fit the line between reduction in LDL cholesterol and reduction of the ratio of major vascular events in the CTT trial with statins [9].

Apo E phenotypes. Cholesterol absorption and synthesis

The extent of LDL-cholesterol lowering by atorvastatin is similar in men and in women. However, men carrying the epsilon2 allele had a significantly higher mean LDL-C response (-44%) than epsilon3 homozygotes (-37%) and epsilon 4 carriers (-34%); P = 0.01). No such interactions between genes and treatment were noted in women. Those carrying the epsilon2 allele showed a similar mean response (-34%) as epsilon3 homozygotes (-39%) and epsilon4 carriers (-34%). Mean plasma triglyceride lowering with atorvastatin was 17%.

The effects of the phenotypes of apo E on cholesterol absorption and synthesis are shown in the figure 1.

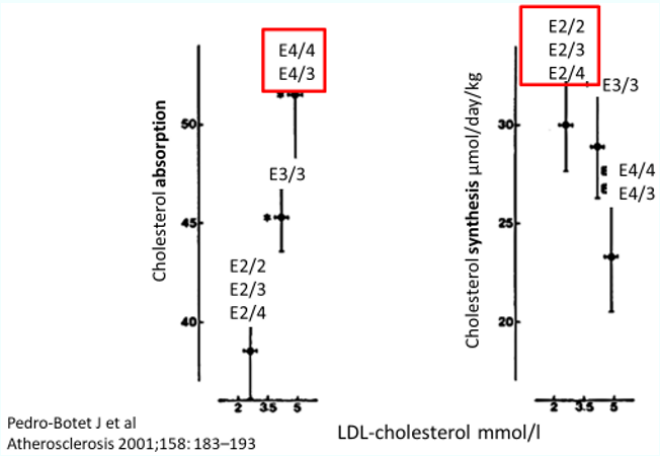

Figure 1: *Apo E phenotypes, cholesterol absorption (left side) and cholesterol synthesis (right side= (modified according to [10].*

Apolipoprotein A IV an important protein for the control of food intake

Apolipoprotein A-IV (apo A-IV) is primarily synthesized in the small intestine and is secreted into intestinal lymph during fat absorption. In the circulation, apo A-IV is present on chylomicron remnants, high-density lipoproteins and also in lipid-free form. ApoA-IV is involved in several physiological processes such as lipid absorption and metabolism, anti-atherosclerosis, platelet aggregation and thrombosis, glucose homeostasis, and food intake [11]. ApoA-IV deficiency is associated with atherosclerosis and diabetes. Intestinal apo A-iV only responds to the uptake of lipids and not of other micronutrients. The rapid increase of circulating apo A-IV is consistent with its involvement in the short time regulation of the saturation and the glucose homeostasis by stimulation of the insulin secretion by the pancreas.

High absorbers and overproducers - Clinical consequences

In a post hoc analysis of the 4S trial the efficacy of simvastatin treatment was evaluated according to the rate of cholesterol absorption [12]. With increasing quartile of cholesterol absorption, the response to statin decreased and the percent of coronary events in the patients under treatment with simvastatin increased. This indicates that simvastatin was most efficacious in patients with lowest amount of cholesterol absorption. The risk in the highest quartile for cholesterol absorption was 2.2 times greater than in the lowest quartile.

Patient with a high basal ration of cholestanol/cholesterol have a high absorption rate for cholesterol and do not profit from a statin alone therapy.

Counter regulation of cholesterol synthesis and cholesterol absorption

Statins decrease cholesterol synthesis in the liver concomitantly cholesterol absorption is increased as a counter regulation. On the other hand ezetimibe inhibits cholesterol absorption in the intestine and as a counter regulation synthesis in the liver is increased. An increase in the statin dose increases the counter regulation and increases the resorption of cholesterol from the intestine [13]. Therefore, a cholestanol guided LDL cholesterol-lowering therapy was proposed: synthesizers should be treated by statin monotherapy, the mixed group by statin plus ezetimibe and high absorbers by ezetimibe alone (eventually combined with bile acid binding resins [14]. By determining whether a patient is mainly a synthesizer or an absorber of cholesterol, customized regimens can be used and are expected to improve patient outcomes and minimize costs of treatment.

Conclusion

Around 15% of the general population are extreme “high absorbers” and 2% are extreme “overproducers” of cholesterol, i.e. the proportion of cholesterol absorption or cholesterol synthesis respectively exceeds 70%.

High cholesterol absorbers almost do not respond to statin therapy.

Cholesterol overproducer efficiently respond to statin treatment, while the cholesterol absorption inhibitor ezetimibe is less effective.

Statin therapy increases cholesterol absorption, while treatment with ezetimibe increases cholesterol synthesis.

By determining whether a patient is mainly a synthesizer or an absorber of cholesterol, customized regimens can be used and are expected to improve patient outcomes and minimize costs of treatment.

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