

## Fibrates & Reduced HDL-C

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Normally fibrates slightly increase HDL-C through a variety of mechanisms although I have seen in some of my patients and I get e-mails asking why fibrates seem to drop HDL-C in some patients.

Here is the current knowledge of how fibrates influence HDL-P, HDL size and HDL-C:

- 1) Increased hepatic apoA-I and apoA-II production (PPAR-alpha mediated)
- 2) Decreases TG production via increased beta-oxidation of fatty acids and decreased FA synthesis, and inhibition of DGAT2 (the enzyme changing diacylglycerol to triacylglycerol). Less TG will be available to the VLDL particle and CETP activity will be reduced thereby causing less CETP-mediated delipidation of HDL. Increasing apoA-V via PPAR-alpha agonism also reduces TG synthesis.
- 3) Increased Lipoprotein Lipase and apoA-V production and decreased apoC-III production: this enhances catabolism (lipolysis) of apoA-I carrying chylomicron particles: i.e. plasma apoA-I is further increased.
- 4) Increased upregulation of ABCA-I (via PPAR alpha enhancement or cross talk with liver X receptor function) which enhances HDL particle lipidation in tissues especially the liver
- 5) Upregulation of hepatic SR-B1 enhancing delipidation of large cholesterol-rich HDL particles, creating smaller HDL particles.

However patient responses to PPAR alpha agonists are very individual (people have variable response elements or polymorphisms on their DNA genes), so some people seem to get more SR-B1 upregulation than apoA-I production and there might be a drop in HDL-C: but who cares, as the cholesterol is being excreted in the bile (enhancing direct reverse cholesterol transport).

Dramatic HDL-C lowering has been described in a few people where fenofibrate is combined with rosiglitazone (Avandia) which also has the potential to upregulate SR-B1. Sometimes the HDL-C goes extremely low on this combo. Some have termed this the disappearing HDL syndrome.

With regard to statins, keep in mind that Lipitor (atorvastatin) is an unusual statin that as you increase the dose above 40 mg the HDL-C increment that occurs with the 10 mg dose disappears and may reduce, yet atorvastatin clearly reduces clinical events in persons with low HDL-C. Probucol a powerful antioxidant that prevents arterial restenosis is a CETP and SR-B1 inducer that dramatically reduces HDL-C (by 20-30%).

In the VA-HIT trial gemfibrozil increased total HDL-P (using NMR analysis), but shifted LDL size from large to small (as it was inducing particle delipidation). If one increases HDL particle count but reduces the size of HDL particles, HDL-C can drop, stay the same or minimally increase. In VA-HIT there was a 10% rise in HDL-P but only a 6% (1.8 mg/dL) rise in HDL-C and this was associated with the positive clinical outcome.