

# Pitavastatin versus Atorvastatin: Potential Differences in their Effects on Serum Lipoprotein Lipase and Cardiovascular Disease

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See article vol. 29: 451-463

Currently, pitavastatin (PIT) and atorvastatin (ATO) are widely used statins in daily practice of hypercholesterolemia treatment because of their effectiveness in lowering serum low-density lipoprotein cholesterol (LDL-C)<sup>1,2</sup>. Numerous pieces of evidence have demonstrated that they are highly effective in preventing the development of atherosclerotic cardiovascular disease (ASCVD)<sup>3-5</sup>. It remains to be clarified whether there are any differences in the degree for ASCVD prevention by PIT and ATO.

Lipoprotein lipase (LPL) is a lipolytic enzyme involved in catalyzing the hydrolysis of triglycerides (TG) in chylomicrons and very low-density lipoprotein (VLDL) particles.

Over the last few decades, increasing attention has been paid to the clinical significance of measuring serum LPL protein mass. Several clinical studies have shown that increased LPL mass is inversely associated with the development of atherosclerosis<sup>6-8</sup>.

Several researchers have paid attention to the effect of statin treatment on changes in serum LPL mass<sup>9-12</sup> or post-heparin plasma LPL activity<sup>13</sup> (**Table 1**).

Among them, several studies have showed that ATO treatment is associated with no changes<sup>9</sup> or increases<sup>10</sup> in serum LPL mass or post-heparin plasma LPL activity<sup>11</sup>, whereas PIT treatment is associated with increased LPL mass. Interestingly, Kakuda *et al.*<sup>12</sup> have shown by directly switching from ATO (10 mg/day) to PIT (2 mg/day) treatment that PIT was more effective than ATO in increasing LPL mass.

In the current issue of *Journal of Atherosclerosis and Thrombosis*, Nagayama *et al.*<sup>12</sup> have reported that PIT reduced CV events more efficaciously than ATO

despite their similar LDL cholesterol-lowering effects and suggested that increased LPL mass during the first year after PIT treatment is associated with this efficacy.

What would be the mechanisms through which PIT treatment is associated with increased LPL mass? Unlike fibrates, statins are not a ligand of peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ); however, a study using rat hepatoma McARH7777 cells showed that PIT increased PPAR $\alpha$  mRNA and its downstream gene expression<sup>14</sup>.

Another potential mechanism underlying increasing serum LPL owing to PIT could be explained by its insulin sensitizing effect. Serum LPL mass has been shown to be a useful parameter for predicting insulin sensitivity<sup>15</sup>. Indeed some study<sup>11</sup> on Japanese hyperlipidemic subjects have shown that 1 mg/day of PIT decreased the HOMA-IR by 13% ( $p < 0.001$ ), which was in stark contrast with ATO being associated with increasing this parameter by +26%.

Next, what would be the mechanisms for the correlation of increased serum LPL with decreased cardiovascular disease? Unlike post-heparin plasma LPL, serum LPL per se does not appear to be catalytically active and thus, its concentration could be a marker for the amount of systemically available (catalytically) active LPL. Serum LPL mass may, however, also have a direct atheroprotective role in mediating the clearance of atherogenic lipoproteins remnants<sup>16</sup>, independent of its catalytic activity. The Epic-Norfolk prospective study<sup>6</sup>, which is mentioned earlier, showed that the observed significantly inverted relation of LPL mass with the incidence of cardiovascular disease disappeared when triglyceride values were adjusted. This indicates that increased LPL mass may contribute to reductions in the incidence of cardiovascular disease by somehow decreasing triglyceride values.

Besides LPL mass, there has been an interesting

**Table 1.** Clinical studies on the effects of pitavastatin or atorvastatin on serum lipoprotein lipase

Authors	year	Subjects	Statin	Serum LPL
Kobayashi <i>et al.</i> <sup>9)</sup>	2001	Hyperlipidemia ( <i>n</i> = 21)	ATO (10 mg/day)	No change
Endo <i>et al.</i> <sup>10)</sup>	2004	Type 2 diabetes ( <i>n</i> = 24)	ATO (10 mg/day)	increased
Schneider <i>et al.</i> <sup>13)</sup>	2004	Type 2 diabetes ( <i>n</i> = 61)	ATO (40 mg/day)	*increased
Kakuda <i>et al.</i> <sup>11)</sup>	2014	Dyslipidemia ( <i>n</i> = 129)	PIT (2 mg/day)	increased
Nagayama <i>et al.</i> <sup>12)</sup>	2021	hypercholesterolemia ( <i>n</i> = 107)	PIT (2 mg/day)	increased
		hypercholesterolemia ( <i>n</i> = 116)	ATO (10 mg/day)	No change

LPL, lipoprotein lipase; ATO, atorvastatin; PIT, pitavastatin

\*lipoprotein lipase activity in post-heparin plasma

study comparing the effect of ATO and PIT on serum lipids<sup>17)</sup>. They reported that serum high-density lipoprotein cholesterol (HDL-C) levels increased after 1, 3, and 6 months of PIT, whereas it was decreased even after 6 months of ATO, suggesting that PIT is superior to ATO in changes in serum HDL-C levels. This finding is in line with the report in clinical practice that PIT was associated with an increase in serum HDL-C level<sup>2)</sup>.

In conclusion, PIT may have additional favorable effects on serum lipid and lipolytic enzyme levels compared with ATO, leading to further antiatherogenic effects.

### Conflicts of Interest

None.

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