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## Effect of Statins on Biliary

### Lipids and Cholesterol Gallstones

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# Effect of Statins on Biliary Lipids and Cholesterol Gallstones

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**Abstract:** This article reviews the effect of statins on biliary lipids with a particular focus on cholesterol gallstones. Pathogenesis of cholesterol gallstones is primarily due to an altered lipid metabolism giving rise to a greater proportion of cholesterol relative to other bile lipids being secreted from the liver into bile. Conflicting reports exist on the effect of statins on biliary cholesterol saturation and this is partly due to the difficulty in obtaining appropriate bile samples from suitable patients. Critical evaluation of the literature from 1988 to 2001 indicates that there is compelling evidence that statins decrease the cholesterol saturation of bile, through the selective reduction in biliary cholesterol secretion. The reduction in biliary cholesterol saturation does not appear to be related to duration of statin therapy, whether the patient group is normo- or hypercholesterolaemic, or whether the bile samples were obtained via the duodenum or directly from the gallbladder. There was, however, good evidence suggesting that basal cholesterol saturation indices in the desirable range are not altered or show minimal decrease by statins. Beneficial clinical outcomes in patients with cholesterol

gallstones are limited to isolated reports of slight reduction in gallstone size and cases of gallstone dissolution. A combination of statin and ursodeoxycholic acid appears to produce a synergistic effect. Statin therapy may be considered as an alternative to surgery or in patients at high risk for cholesterol gallstones. The data also suggest that patients in whom a choleric effect is required may benefit from statin therapy.

**Kurzfassung: Der Einfluß von Statinen auf Gallensteine und die Lipidzusammensetzung der Galle.** Diese Übersichtsarbeit behandelt die Wirkung von Statinen auf die Lipidzusammensetzung der Galle und auf die Cholesteringallensteine. Die Pathogenese der Cholesteringallensteine wird hauptsächlich von einem abgeänderten Lipidmetabolismus verursacht, der den Anteil von Cholesterin im Verhältnis zu den anderen von der Leber in die Galle sezernierten Lipiden erhöht. Die Lipidzusammensetzung der Galle ist wichtig für die Entstehung von Gallensteinen. Es existieren unterschiedliche Ergebnisse bezüglich Cholesterinsättigung der Galle unter Statintherapie. Diese Unterschiede sind haupt-

sächlich auf die Schwierigkeiten, geeignete Galleproben zu bekommen, zurückzuführen. Wenn man die Ergebnisse aller Studien von 1988–2001 zusammenfaßt, kommt man zu dem Schluß, daß Statine die herabgesetzte Cholesterinsättigung der Galle über eine verminderte Cholesterinsekretion in die Galle bewirken. Dieser Effekt scheint unabhängig von der Dauer der Statintherapie, dem Plasmacholesterinspiegel (normo- oder hypercholesterinämisch) und der Galleentnahmestelle (via Duodenum oder direkt aus der Gallenblase) zu sein. Cholesterinspiegel im Normbereich scheinen unter einer Statintherapie nicht oder nur geringfügig gesenkt zu werden. Es gibt nur wenige kontrollierte klinische Studien, diese allerdings berichten über eine Verkleinerung von Gallensteinen und vereinzelt über das Auflösen von Gallensteinen unter Statintherapie. Eine Kombination von Statin und Ursodesoxycholsäure scheint synergistisch zu wirken. Eine Therapie mit Statinen könnte sich bei Hochrisikopatienten als Alternative zur Operation entwickeln. Die Daten weisen außerdem darauf hin, daß Patienten, die einer Cholelithotomie bedürfen, von einer Statintherapie profitieren. **J Kardiologie 2002; 9: 295–8**

## Introduction

The statin class of drugs has revolutionised the treatment of hypercholesterolaemia. Statins effectively lower plasma low-density lipoprotein (LDL) cholesterol and markedly reduce the incidence of and the mortality from ischaemic coronary events [1–3]. The effect of statins on biliary lipids has received much less attention possibly due to the relatively less benign nature of diseases related to bile. Only one review article in this area has been published [4] and many original research articles have been published since then, making the present review timely. The most common disease associated with biliary lipid abnormalities is cholesterol gallstones. Cholesterol gallstone disease and coronary artery disease are related in that there is an inverse association between plasma cholesterol levels and cholesterol gallstones [5–7]. In addition, data extracted from the Framingham study showed a significant positive association between diagnosed cholesterol gallstone disease and subsequent incidence of coronary heart disease in men but not in women [8].

The prevalence of cholesterol gallstones in developed countries is 5–80 % depending on geographical location and ethnic background. Approximately 20 % of subjects with gallstones will get symptomatic requiring treatment, which at present most often involves the surgical removal of the gallbladder and stones (cholecystectomy). It is now widely accepted that the primary event in the pathogenesis of chole-

sterol gallstones is an altered lipid metabolism giving rise to a greater proportion of cholesterol relative to other bile lipids being secreted from the liver into bile [9]. The co-existence of nucleating factors, gallbladder hypomotility and mucus hypersecretion also contribute to cholesterol precipitation and gallstone development [9]. An abnormality in lipid metabolism may arise from a combination of a number of different factors such as excess dietary cholesterol/fat, obesity, diabetes and genetic factors. Genetic aspects are exemplified by the studies involving North American Indians [10] and Caucasian family members of affected individuals [11–14].

Statins entered the market at a time when other plasma cholesterol lowering drugs, such as the fibrates were known to increase the cholesterol saturation of bile [15–18] and the incidence of gallstones [19, 20]. So initially there was concern that statins may also produce a similar effect. However this has been shown not to be the case. As statins decrease cholesterol synthesis through competitive inhibition of the rate-limiting enzyme (HMG-CoA reductase), logic suggests that the amount of cholesterol available for secretion into plasma and/or bile will decrease. Whereas, a reduction of cholesterol secretion in plasma often results in a decrease in plasma LDL, a reduction in the secretion of cholesterol in bile likely results in a more favourable biliary lipid profile that may prevent cholesterol gallstone development/growth or even dissolution of cholesterol stones.

### Abbreviations:

**CSI** = cholesterol saturation index; **FH** = familial hypercholesterolaemia; **HMG-CoA** = 3-hydroxy-3-methylglutaryl-coenzyme A; **LDL** = low density lipoprotein; **LI** = lithogenic index, **NS** = not significant; **VLDL** = very low density lipoprotein

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To date a number of conflicting reports have been published on the effect of statins on biliary cholesterol saturation (see below) and this is in part due to the difficulty in obtaining appropriate bile samples from suitable patients that reflect hepatic synthesis and secretion. Therefore aspects of bile sampling and the study population investigated will be considered in more detail below. Published studies on the effect of statins on cholesterol gallstone dissolution are limited. However there are encouraging reports of cholesterol gallstone dissolution with statins alone or in combination with other agents. These will be discussed in context below.

### ■ Biliary Lipid Concentrations, Cholesterol Saturation Index and Cholesterol Gallstones

The liver and biliary system are particularly important in cholesterol homeostasis. Firstly, the liver not only synthesizes cholesterol, bile acids and phospholipids, but it also assembles and secretes lipoproteins such as very low density lipoproteins (VLDL), which is subsequently catabolized to LDL in plasma. Secondly, among other molecules, the liver secretes cholesterol, bile salts and phospholipids in bile and this mechanism is the major removal pathway for cholesterol from the body. Individuals are predisposed to cholesterol gallstones if their bile has an increased proportion of cholesterol relative to its two more hydrophilic lipids, bile acids (salts) and phospholipids. This relative proportion of lipids is known as the cholesterol saturation index (CSI) or lithogenic index (LI) and is the major indicator determining whether bile is *over-saturated* with cholesterol (CSI > 1.0) or within *desirable* levels (CSI < 1.0). CSI > 1.0 is a prerequisite for cholesterol gallstone formation. Thus, cholesterol gallstones cannot develop if the CSI is < 1.0 and frequently form if CSI is > 1.0.

### ■ Bile Samples Used to Examine the Effect of Statins on Biliary Lipids

Due to the invasiveness of some procedures, technical difficulty with other procedures and ethical concerns, bile samples used to examine the effect of statins on biliary lipids have been collected from several regions of the biliary system. For studies to be considered in this review, bile samples were obtained from one of the following locations and occasionally from two of these simultaneously:

- directly from the gallbladder at operation for gallstones
- from the common bile duct (hepatic bile) using a cholangiogram catheter
- from a "T-tube" (hepatic bile) placed in the common duct at surgery or
- from the common bile duct via the duodenum (duodenal bile) following an intravenous injection of cholecystokinin

The choice of sampling method is dictated by a combination of factors, such as, the patient group, technical expertise and ethical considerations. As mentioned by Strasberg, Harvey and Hofmann [21] every technique involves some compromise. Bile collected via the duodenum avoids the effects of

anaesthesia, drugs and for control samples, intercurrent diseases. The disadvantage is that the duodenal sample is a mixture of gallbladder and hepatic bile and intestinal secretions. Hepatic bile collected by catheter or T-tube often provides an uncontaminated sample if obtained with care. In sampling gallbladder bile from patients with gallstones, one must have knowledge of the state of the disease. The gallbladder must be functioning and complications such as acute cholecystitis or acute pancreatitis must be excluded as these conditions substantially alter bile composition.

### ■ Effect of Statins on Biliary Cholesterol Saturation Index (CSI)

Table 1 summarises the results of the effect of five different statins on biliary cholesterol saturation with an emphasis on the type, dose and duration of statin, the study population investigated, and the bile sample in which the result was obtained. Of the 18 studies, eight showed that statin treatment resulted in a significant reduction in CSI [22, 23, 25, 28, 30, 31, 34, 39], one almost reached a statistical significant decrease [24], another showed a significant decrease in hepatic bile CSI but not gallbladder CSI [36], and eight studies showed no change [26, 27, 29, 32, 33, 35, 38, 40]. Of the studies showing no change, five had patient cohorts that had all or a significant proportion of their basal CSI's in the desirable range (CSI < 1.0) [26, 29, 35, 38, 40] and one reported the complete dissolution of gallstones in one of the seven patients [33]. The same authors of one study showing no change in CSI [27] previously had reported the complete dissolution of a cholesterol gallstone with statin therapy [25]. To the authors' knowledge there have been no published studies examining the effect of atorvastatin on biliary lipids.

Eight studies (from Table 1) were performed in patients with confirmed gallstones, presumably cholesterol type, although the cholesterol content of the stones was not reported. Five studies showed reductions in CSI, four significant [25, 34, 36, 39] with decreases in hepatic bile but not in gallbladder bile in one study [36], and one close to statistical significance [24]. These results highlight that those patients with cholesterol saturated bile (*i.e.* cholesterol gallstone patients) are more likely to show a decrease in CSI with statin treatment. To examine this point further we reported the cholesterol content of the gallstones from the patients in whom both gallbladder and hepatic biliary lipids were determined [37]. Stones containing > 50 % cholesterol, by weight, were classified as "cholesterol" type stones and the respective bile samples from only these patients were analysed and reported [36, 37]. The mean cholesterol content in the control gallstone group was 89 % (range 57–100 %) and in the simvastatin group 92 % (range 62–100 %). CSI of gallbladder bile was unchanged between the two groups. However it was markedly decreased in hepatic bile by 27–47 % as judged by two different cholesterol saturation indices. In hepatic bile there was also a 22 % significant reduction in the bile acid hydrophobicity index in statin treated patients compared with controls [36, 37]. Hydrophobic bile acids are known to suppress bile acid synthesis, thus a decrease in these particular bile acids stimulates bile acid synthesis. This leads to a greater transformation of hepatic cholesterol to bile acids inducing a reduction in cholesterol available for biliary secretion.

## Summary and Conclusions

Critical evaluation of the literature spanning years 1988–2001, encompassing five different statins (Table 1), indicates that there is compelling evidence that statins decrease the cho-

lesterol saturation of bile, through the selective reduction in biliary cholesterol secretion [31, 32, 41, 42]. The reduction in biliary cholesterol saturation does not appear to be related to duration of statin therapy, whether the patient group is normo- or hypercholesterolaemic, or whether the bile samples were

**Table 1:** Effect of Statins on Biliary Lipids and Cholesterol Saturation Index (CSI) in Humans

Statin (Dose)	Duration of Statin	Patient Group (No.)	Bile Sample	Change In Cholesterol Saturation Index (CSI) of Bile	Reference
Lovastatin (40–80 mg)	6–13 weeks	Hypercholesterolaemic type IIa and IIb (7)	Duodenal	CSI decreased from 1.045 to 0.883 (16 %); basal CSI > 1.0 for 5 patients	Freeman et al. [22]
Pravastatin (40 mg)	8 weeks	Heterozygous FH (6)	Duodenal	CSI decreased from 1.06 to 0.75 (23 %); CSI decreased 41 % in three with basal CSI > 1.0	Hoogerbrugge-vd Linden et al. [23]
Pravastatin (2 × 20 mg)	3 weeks	Hypercholesterolaemic gallstone patients (6 statin) vs normo-cholesterolaemic gallstone controls (9)	Gallbladder and hepatic	<i>Gallbladder:</i> CSI, NS (p = 0.06) decrease from 1.30 to 0.83 (36 %); molar cholesterol NS 21 % decrease <i>Hepatic bile:</i> 24% NS decrease in CSI	Reihner et al [24]
Pravastatin (40 mg)	3 months	A hypercholesterolaemic male with solitary radiolucent cholesterol gallstone (12 mm)	Duodenal	CSI decreased from 1.3 to 0.8 (38 %). The solitary gallstone totally dissolved	Smit et al. [25]
Pravastatin (20 mg)	1–2 weeks (mean 11 days)	Normocholesterolaemic cholesterol gallstone (6 statin, 7 control)	Gallbladder	CSI unchanged (control 1.09, statin 1.00)	Okamoto et al. [26]
Pravastatin (40 mg)	3 weeks	Hypercholesterolaemic cholesterol gallstone (13 statin vs 14 placebo)	Gallbladder	26 % NS increase in CSI (statin 1.42 vs placebo 1.13); these authors previously reported gallstone dissolution [25]	Smit et al. [27]
Pravastatin (10 mg)	12 months	Type IIa non-FH (18)	Duodenal	CSI decreased from 1.52 to 0.95 (38 %) after 12 months; no difference in CSI at 3 months	Tazuma et al. [28]
Pravastatin (2 × 40 mg)	5 days, then withdrawn	Normo- and moderate hypercholesterolaemic (9 statin, 7 had common bile duct stones, vs 7 placebo, 5 with common duct stones)	T-tube (hepatic bile)	CSI unchanged at day 5 (1.10 vs 1.04); day 7 CSI was 37 % increased and returned to basal thereafter	Muraca et al. [29]
Simvastatin (20 mg or 40 mg)	7–13 weeks	Type IIa and IIb hypercholesterolaemic (10: 7 polygenic and 3 with FH)	Duodenal	CSI decreased from 1.01 to 0.77 (24 %), not dose related; statin increased CSI in one patient; 4 patients had basal CSI > 1.0	Duane et al. [30]
Simvastatin (40 mg)	4 weeks	Gallstone free non-FH (8)	Duodenal	CSI, molar % cholesterol and biliary cholesterol secretion all decreased by 38 % (CSI from 1.51 to 0.94); all basal CSI > 1.0	Mazzella et al. [31]
Simvastatin (40 mg)	4 weeks	Obese normo-lipidaemic subjects (6)	Duodenal	NS decrease in CSI (about 14 %); mean basal CSI about 1.35	Mazzella et al. [32]
Simvastatin (40 mg)	12 months	Hypercholesterolaemic cholesterol gallstones (7)	Duodenal	CSI unchanged (control 1.63, statin 1.59); molar cholesterol, NS decrease by 31 %; biliary secretion of cholesterol NS decrease (n = 5; p = 0.08); gallstones dissolved in 1 patient	Miettinen et al. [33]
Simvastatin (20 mg)	12 months; selected patients 24 months	Hypercholesterolaemic gallstone: diabetics (7) and non-diabetics (4)	Duodenal	CSI decreased from 1.30 to 0.94 (28 %); small decrease in gallstone diameter (three largest reduced by 9 %); statin for 24 months showed no further reduction in stone diameter	Chapman et al. [34]
Simvastatin (20 mg)	3 months	Primary non-FH gallstone free (8)	Duodenal	10 % NS decrease in CSI (CSI increased in 1 patient); 2–3 patients had basal CSI < 1.0	Lanzarotto et al. [35]
Simvastatin (20 mg)	3 weeks	Normocholesterolaemic gallstone (8 statin, 92 % stone cholesterol; 6 controls, 89 % stone cholesterol)	Gallbladder and hepatic	<i>Gallbladder:</i> NS 20 % decrease in CSI (control 1.58, statin 1.27). <i>Hepatic:</i> CSI decreased 27–47 %; hydrophobicity index decreased 22 %; basal CSI > 1.0 for all patients	Smith et al. [36] Smith et al. [37]
Fluvastatin (30 mg)	12 weeks	Hypercholesterolaemic (19: 13 type IIa & 6 type IIb)	Duodenal	CSI no change; majority of basal CSI < 1.0	Tazuma et al. [38]
Fluvastatin (2 × 40 mg)	12 weeks	Mild hypercholesterolaemia and history of gallstones (14 statin vs 7 placebo)	Duodenal	CSI decreased 26 % (statin 1.45, basal 1.97); NS decrease of 17 % in molar % cholesterol	Porsch-Özçürümez et al. [39]
Cerivastatin (0.2 mg)	12 weeks	Hypercholesterolaemic (21: 16 type IIa and 5 type IIb)	Duodenal	CSI unchanged; basal CSI 0.81, statin 0.80	Tazuma et al. [40]

obtained via the duodenum or directly from the gallbladder. There was, however, good evidence suggesting that basal CSI's below 1.0 (i.e. not saturated with cholesterol) are not altered or show minimal decrease by statins.

The notion that decreased cholesterol saturation translates to a beneficial clinical outcome is evidenced by gallstone dissolution by pravastatin [25], the mention of gallstone dissolution with simvastatin [33], and some reduction in gallstone size with simvastatin treatment [34]. Although there is no evidence to support the use of statins in primary or secondary prevention for cholesterol gallstones, its use as an alternative to surgery or in patients at high risk for cholesterol gallstones, such as in some families, cannot be underestimated, particularly in combination with ursodeoxycholic acid, which seems to have a synergistic effect [31, 33, 43, 44]. Both these agents have a beneficial effect on both plasma and biliary lipids. As a cautionary note, as many cholesterol gallstone patients have desirable plasma cholesterol levels (< 5.5 mM; 213 mg/dl) one must be careful not to lower their plasma cholesterol level too much; a level of 3.5 mM (135 mg/dl) could be considered a lower limit. However, plasma cholesterol levels below 3.5 mM are not likely to be a problem because data from large-scale statin trials show no hint of low plasma cholesterol levels being associated with increased adverse events. Whether statins decrease the incidence of gallstone disease is an interesting question and such data should be available from previous studies designed to assess the incidence of and mortality from ischaemic coronary events [1–3]. This information could prove useful and should be extracted if possible. Data from the Framingham study [8] indicates that male gallstone patients are at increased risk for subsequent coronary disease and therefore should be monitored accordingly.

Collectively the effect of statins on bile cholesterol saturation and bile acid hydrophobicity indicate that patients in whom a choleric effect is required, such as patients with biliary stents, may also benefit from statin administration to decrease the severity and quantity of stent blockages that usually accompany this type of surgery. Further research to address this specific issue is warranted.

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