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The Preventive Effect of Vitamin E on Gallstone Formation (3) A Study of the Biliary Lipids in Patients with Gallstones

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Summary

An α-tocopherol soft capsule (100 mg of d-α-tocopherol) was given orally to 12 patients with gallstones. The dosage was 6 capsules daily (200 mg t.i.d.) in 10 of the patients and 1 capsule daily (100 mg, after breakfast) in the other two patients, and these dosages were maintained for 4 consecutive days. In patients receiving 600 mg daily and in whom the T-tube was kept closed all day except for 5 minutes in the early morning (the concentration study group), showed serum α-tocopherol levels of 27–43 μg/ml. In patients whose bile was retained in the bag for 24 hours (the excretion study group), the serum α-tocopherol level remained at 12.6 μg/ml. In five patients with cholesterol gallstones, the 600 mg/day α-tocopherol administration reduced biliary cholesterol levels and increased glycine-conjugated bile acids. A corresponding improvement of the lithogenic index was observed in all five patients. On the other hand, in the two patients of excretion group whose T-tubes were not closed at the beginning of this study, in the two patients with bilirubin stones, and in a patient who underwent total gastrectomy, the above effects of α-tocopherol were not observed, despite the daily dose of 600 mg. In the two patients receiving 100 mg of α-tocopherol daily, these effects were also not observed. It was suggested that α-tocopherol may be clinically useful in mono-therapy or combination therapy of gallstone dissolution with CDCA and/or UDCA, recommended for prophylaxis of recurrence after complete dissolution. However, low doses of α-tocopherol in patients with cholesterol stones and patients with other stones were not effective.

Introduction

It has previously been confirmed that, in hamsters α-tocopherol produces a decrease in biliary cholesterol, an increase in GCDCA (glycochenodeoxycholic acid), and a corresponding improvement in the lithogenic index[33,34]. It was also found to prevent cholesterol gallstone formation, and a definite inverse correlation was observed between α-tocopherol concentration

Key words: α-Tocopherol, Gallstone, Serum α-tocopherol concentration, Bile acid, Lithogenic index.
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in the liver and the lithogenic index of the bile. Furthermore, α-tocopherol was shown to ameliorate increased serum cholesterol, triglyceride (TG) and VLDL levels. In the present study, the effects of α-tocopherol on the biliary lipids and serum lipids in human were evaluated. Since the α-tocopherol solution used on hamsters contained polyethylene glycol and hydrogenetic caster oil, a synthesized α-tocopherol capsule was used for clinical application.

Materials and Methods

Soft capsules containing 100 mg of d-α-tocopherol and 140 mg of vegetable oil were synthesized by Eizai pharmaceutical Co. (Japan) and the recovery rate for α-tocopherol was more than 99.9% by HPLC.

A total of six men and six women, all of whom were cholecystectomized and fitted with an indwelling T-tube were used (Table 1). The study was performed 10–12 days after the operation, when the enterohepatic circulation of bile acid was nearly normalized. 600 mg (200 mg t.i.d.) daily of α-tocopherol was given to 10 patients, consisting of 8 patients with cholesterol stones and 2 patients with bilirubin stones, and 100 mg of α-tocopherol was given daily, after breakfast, to 2 patients with cholesterol stones.

In every patient except two (Cases 7 and 8), the T-tube was clamped three days before the study, to normalize the enterohepatic circulation. Two different sample collection procedures were carried out. In the concentration study group (Cases 1 to 3 and 9 to 12), 5 ml of bile were obtained from the T-tube every early morning during the study and the T-tube was kept clamped at other times in order not to lose bile acid. In the excretion study group (Cases 4 to 8), 5 ml

Table 1. Background of the patients

No.	Age	Sex	Classification of stone	Body Weight (kg)	Daily dosage of α-tocopherol (mg/kg bw)	T-tube
1	67	F	cholesterol	63.0	600mg (9.5)	closed
2	41	M	cholesterol	56.5	600 (10.6)	closed
3	49	M	cholesterol	62.7	600 (9.6)	closed
4	61	M	cholesterol	59.0	600 (10.2)	open
5	72	M	cholesterol	50.5	600 (11.9)	open
6	54	M	cholesterol	72.0	600 (8.3)	open
7	28	F	cholesterol	56.0	600 (10.7)	open
8	30	F	cholesterol	56.0	600 (10.7)	open
9	67	F	bilirubin	43.8	600 (13.7)	closed
10	58	M	bilirubin	58.5	600 (10.3)	closed
11	48	F	cholesterol	43.0	100 (2.3)	closed
12	46	F	cholesterol	51.6	100 (1.9)	closed

of bile were obtained every morning from the bile collected in the bag for 24 hours.

Sample preparation, determination of bile acid using HPLC in combination with 3α-hydroxysteroid dehydrogenase (3α-HSD)[33], and assessment of biliary cholesterol and phospholipids by enzymatic assay[12,31] were used as in relevant previous studies. The lithogenic index was calculated using the formula of THOMAS and HOFMANN based on the limits of cholesterol solubility defined by SMALL and ADMIRAND[43]. Serum tocopherol concentration was measured by HPLC[1]. Serum lipids and liver function tests were evaluated before, during, and 14 days after administration. Total cholesterol, free cholesterol, phospholipids (PL), triglyceride and β-lipoprotein were determined as serum lipids. GOT, GPT, alkaline phosphatase (ALP) and serum bilirubin were evaluated with conventional liver function tests.

Results

(1) Serum tocopherol

Figure 1 shows that in the patients of concentration study (Cases 1, 2 and 3) receiving 600 mg of α-tocopherol serum α-tocopherol concentration remarkably increased. However, in

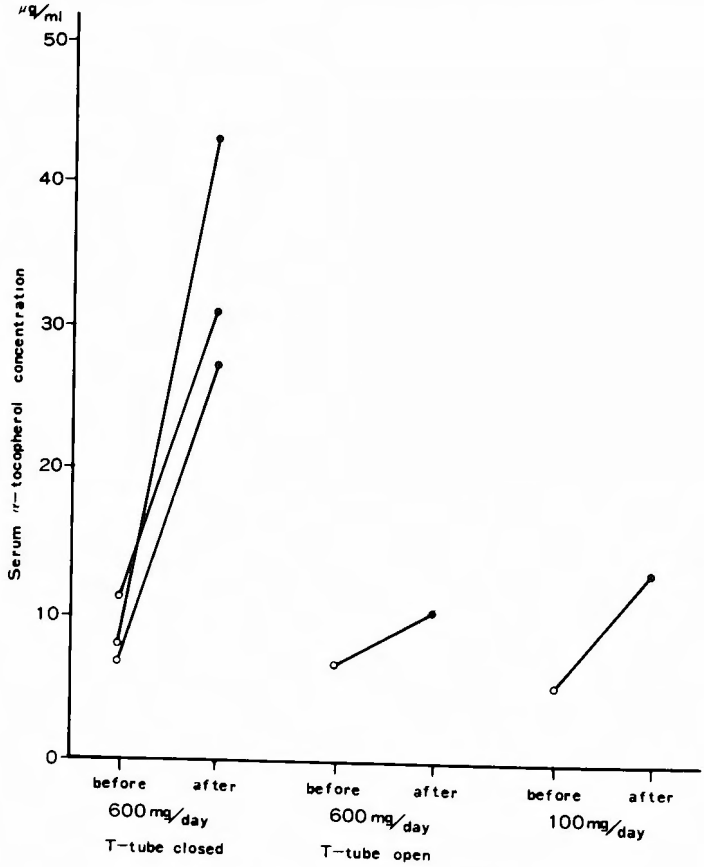

Fig. 1. Serum α-tocopherol concentration

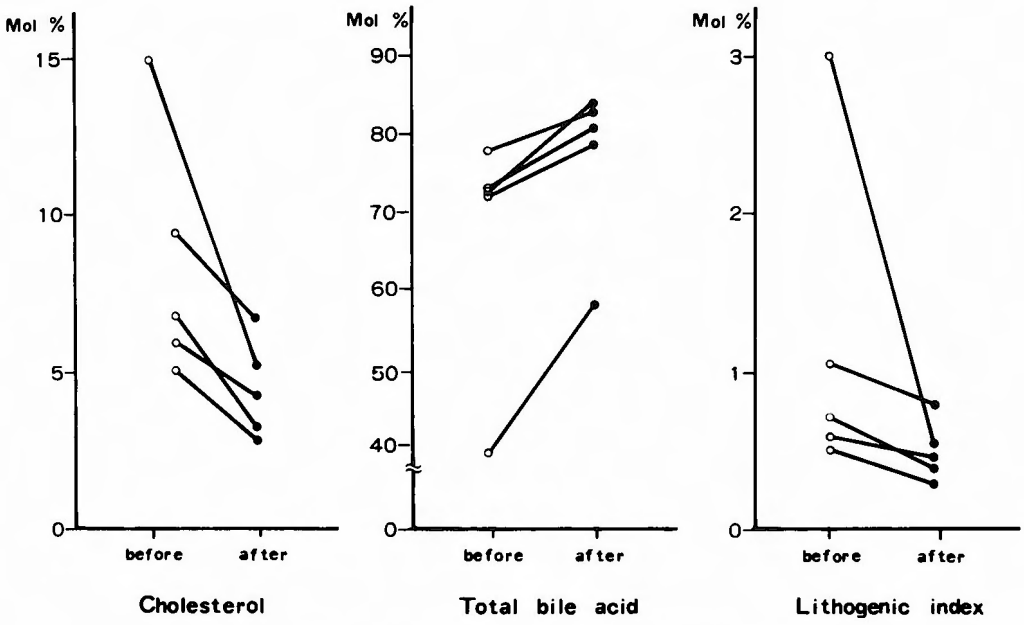

Fig. 2. Biliary lipids of patients in Group I

the patients of excretion study (Case 6) the increase of serum α-tocopherol was moderate to 12.6 μg/ml and the value was equal to that of the concentration study (Case 12) receiving 100 mg of α-tocopherol. In Case 7, this data was not shown in Figure 1, serum α-tocopherol concentration remained at 7.80 μg/ml, although its concentration at the start of the study was not measured. On the other hand, serum β-and γ-tocopherol concentration decreased in all 6 patients.

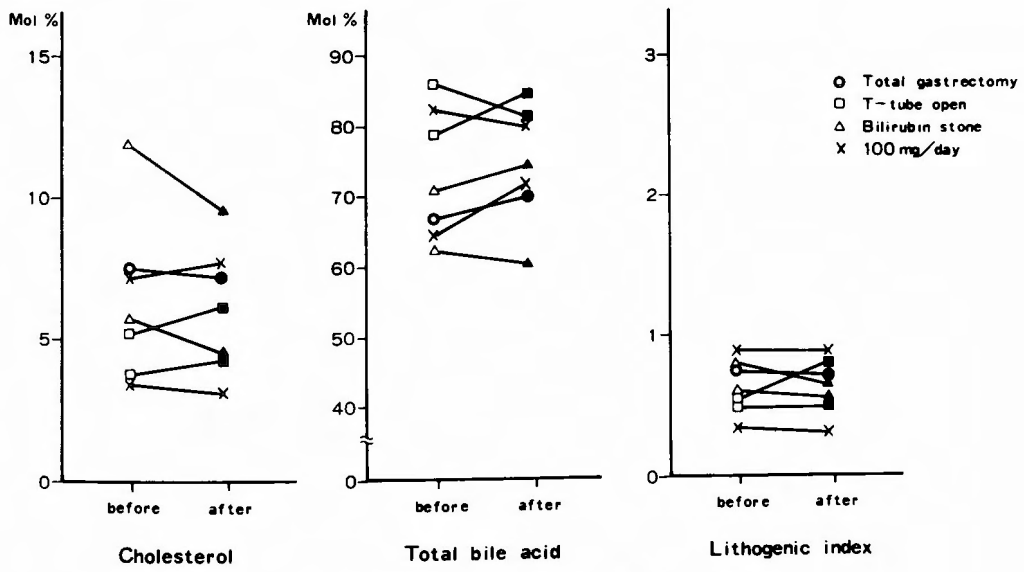

Fig. 3. Biliary lipids of patients in Group II

(2) Biliary cholesterol and phospholipids

From the serum α-tocopherol levels, it seemed that the effect of α-tocopherol on biliary lipids in Cases 6, 7, and 8 was not so effective as in Cases 1 to 5. Thus, Cases 1 to 5 were regarded as an effective group (Group I), while Cases 6 to 8, Cases 9 and 10 with bilirubin stones, and Cases 11 and 12 who received 100 mg of α-tocopherol daily were regarded as belonging to the ineffective group (Group II). α-Tocopherol administration resulted in a decrease of biliary cholesterol in all the Group I patients (Fig. 2), while this decrease was observed in 57% of Group II (Fig. 3). Two patients (Cases 7 and 8) from the excretion group showed an increase in biliary cholesterol level.

Biliary phospholipid concentration increased in 40% of Group I and in 29% of Group II.

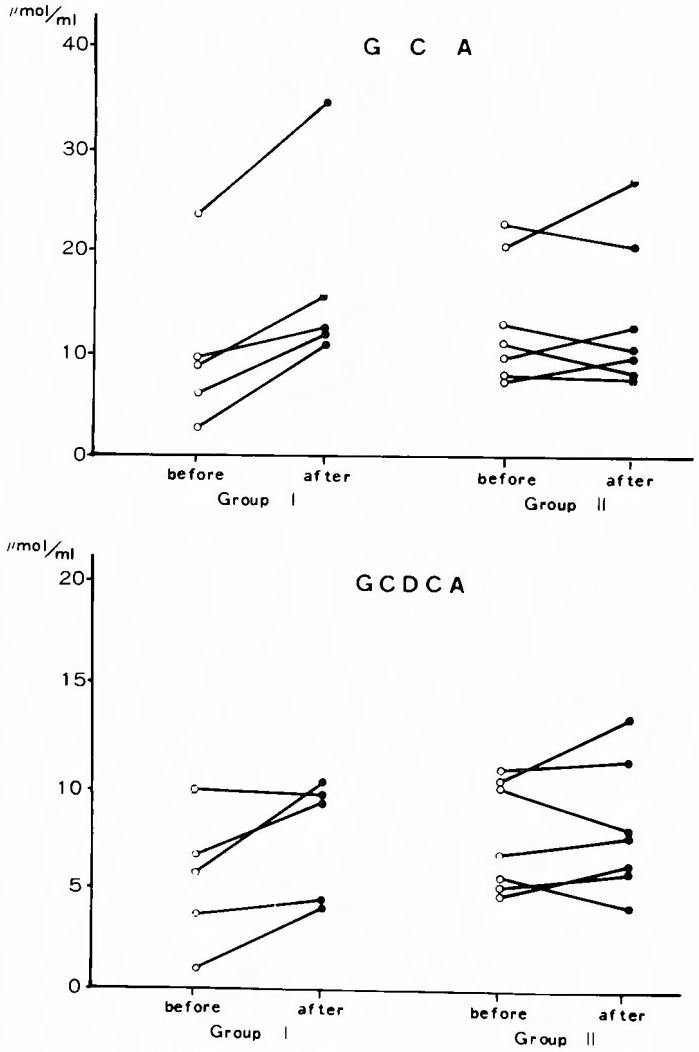

Fig. 4. GCA and GCDCA concentration in hepatic bile

(3) Composition and concentration of bile acids in bile

α-Tocopherol administration resulted in an increase of total bile acid concentration (TBA) in 100% of Group I and an increase of TBA in 57% of Group II (Fig. 3). α-Tocopherol administration caused an increase of glycine-conjugated bile acid concentration in 100% of Group I and 43% of Group II. Neither cases with bilirubin stones nor cases receiving 100 mg of α-tocopherol daily in Group II showed an increase of glycine-conjugated bile acid. Taurine-conjugated bile acid or unconjugated bile acid concentration remained unchanged in almost all cases. An increase in GCA (glycocholic acid) was observed in 100% of Group I and an increase in GCDCA was observed in 80% (Fig. 4). However, in Group II, the increase in GCA was only 43% and that in GCDCA was 57%.

The alteration in the lithogenic index varied according to the dosage of α-tocopherol. The lithogenic index dropped markedly in 100% of Group I (Fig. 2), while an improvement in the lithogenic index was observed in 29% of Group II (Fig. 3).

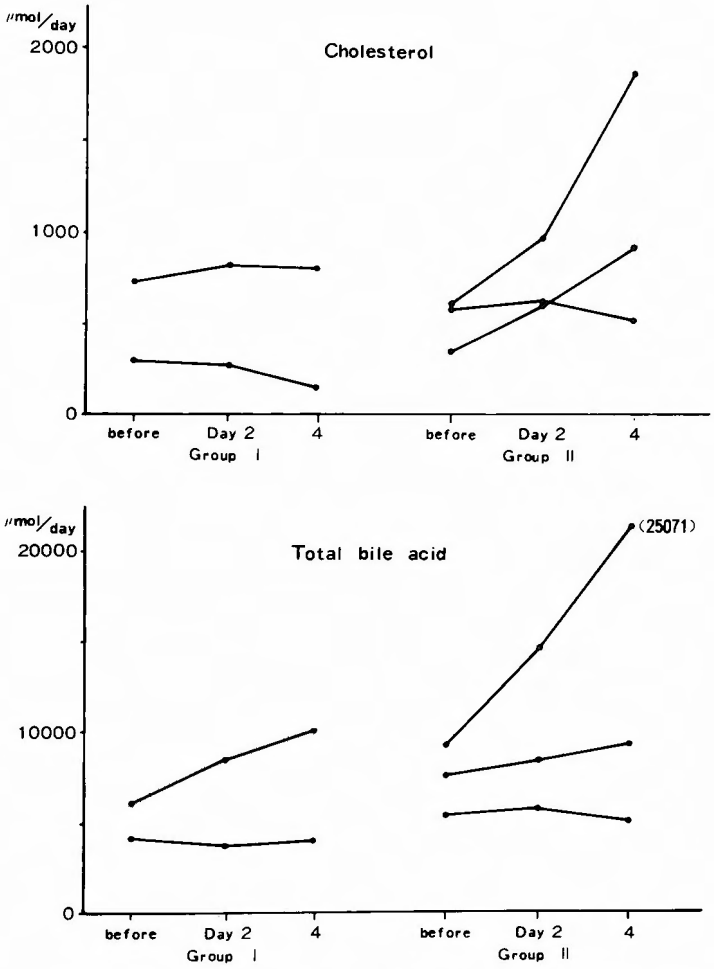

Fig. 5. Daily output of biliary cholesterol and total bile acid

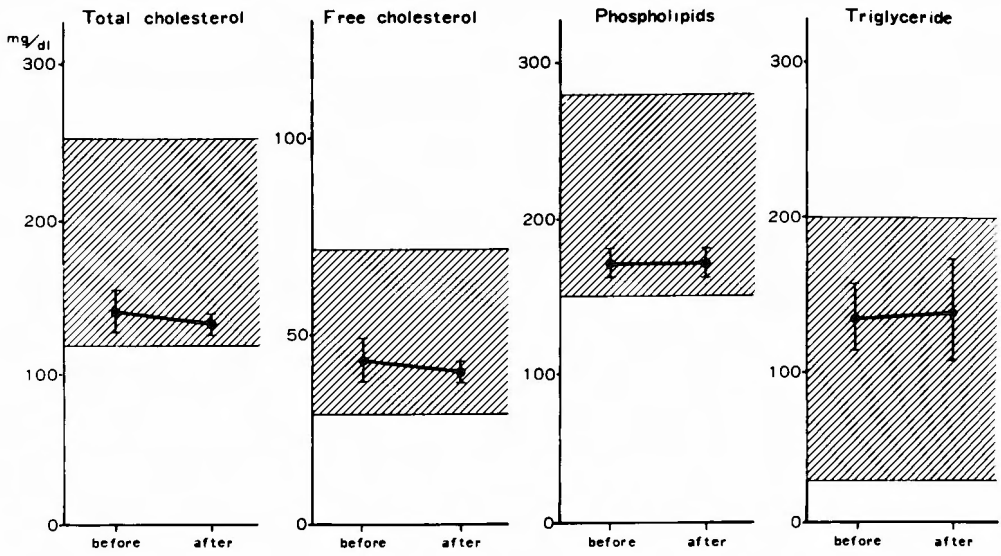

Fig. 6. Changes in serum lipids of 12 patients who received α-tocopherol capsules

(4) Hepatic output of biliary lipids

Hepatic output of biliary lipids was evaluated in five patients (Cases 4 to 8) with cholesterol stones who received 600 mg. The amount of biliary cholesterol secreted (μmol/day) decreased in one of the two cases in Group I, but showed a marked increase in two of the three cases in Group II (Fig. 5). An increase in bile acid secretion was observed in one of the two patients in Group I. A marked increase in bile acid secretion was also seen in the two young cases with a remarkable increase in cholesterol secretion (Cases 7 and 8). An increase in phospholipid output was observed in one of the two cases in Group I and two of the three cases in Group II.

(5) Serum lipids and liver function tests

Among the 12 patients in whom serum lipids were analysed before and during this study, TG was elevated above normal in one patient, total cholesterol reduced below normal in two patients, and PL reduced in two patients before the start of the study. During α-tocopherol intake the elevated TG decreased to within the normal range in one patient, but in the other 11 patients the reduced total cholesterol and PL remained unchanged (Fig. 6). Of the 16 laboratory tests carried out before and during this study, GOT was elevated above normal in nine patients, GPT in nine, ALP in nine, and direct bilirubin in three, before the start of the study. During α-tocopherol intake the elevated GOT decreased to within the normal range in three patients, and GPT normalized in two patients, ALP in three, and direct bilirubin in three. The results of the other tests remained within the normal range in all cases. As observed in hamsters, α-tocopherol was found to ameliorate the increases in liver function parameters such as GOT, GPT, and ALP. No side effects were observed during the study.

Discussion

REWBRIDGE was the first who reported the unexpected disappearance of gallstone shadows in patients receiving exogenous bile acids in 1937[32]. THISTLE and SCHOENFIELD hypothesized that the cholesterol-supersaturated bile in cholesterol gallstone patients was related to the observed decreased bile acid pool. Thus, these patients with gallstones were given one of several different purified bile acids in an attempt to expand the bile acid pool. Of the bile acids tested, only CDCA produced the desirable desaturation of bile[41]. DANZINGER and these investigators treated seven patients with radiolucent gallstones and found dissolution in four of them after 6 to 24 months of CDCA therapy[11] Several studies in many patients with radiolucent gallstones were reported[42,7]. At present, gallstone dissolution with CDCA is available for general medical use around the world, including Japan, where not only CDCA but also UDCA are available. The efficacy of complete or partial dissolution with UDCA or CDCA has usually been less than 40% in Japan, while the efficacy with CDCA in foreign countries has been considerably higher. This difference was assumed to be because the dosage of CDCA in Japan has been low (less than 750 mg per day) in contrast with those of foreign countries[5,18]. Although high doses of CDCA seem to be very effective, the incidence of side effects such as diarrhea or liver dysfunction[37] is also increased. Diarrhea especially, has been observed in at least 40% of cases[30], and usually more than 50%[19,24].

Thus, there is need for an alternative substance, that not only aids the dissolution of gallstones, but also has few side effects, even after long-term administration. To date, a variety of substances have been evaluated with respect to their ability to improve the lithogenic index of the bile. Becobrate reduced billiary cholesterol, while bile acid was simultaneously significantly reduced[21]. Nicotinic acid reduced serum cholesterol level, but also promoted gallstone formation[4]. Although HCA[21] reduced the incidence of gallstone formation, biliary cholesterol level increased and the lithogenic index deteriorated[26]. Cholestyramine reduced biliary cholesterol, and improved the lithogenic index, but accelerated HMG-CoA reductase activity. Although cicloxilic acid reduced biliary cholesterol outputs, and the output of bile acid, HMG-CoA reductase or cholesterol 7α-hydroxylase activity remained unchanged[9,29]. None of the above substances could be applied clinically.

On the other hand, it was previously confirmed that α-tocopherol produces a decrease in biliary cholesterol, an increase in bile acids, and a corresponding improvement of the lithogenic index in hamsters, whose hepatic HMG-CoA reductase activity was raised. In addition, α-tocopherol prevented gallstone formation in half of the animals, and ameliorated the liver function deterioration. Thus, clinical application of α-tocopherol was evaluated.

The study was begun at the 10th postoperative day in order to minimize operative effects, and avoid the disordered enterohepatic circulation of bile acids. Two different methods of collecting hepatic bile (the concentration group and the excretion group) were tried to clarify the effects of α-tocopherol, not only on the concentration but also the outputs of biliary lipids. Serum α-tocopherol concentration was measured to confirm the absorption of α-tocopherol, and

to evaluate its serum level, which can indicate the pharmacological effect. The serum α-tocopherol concentration in the patients of concentration group was 27～43 μg/ml, while in the excretion group it was 12.6 μg/ml. Serum α-tocopherol concentration in the normal subjects without any diseases was 10.1±2.3 μg/ml[39] or 10.5±3.2 μg/ml[17]. From the results of the present study, it appears that a dosage of α-tocopherol sufficient to at least double the normal serum level is necessary to produce a pharmacological effect. This result is in agreement with the results of the experimental animal models[33,34], or with the results of HARMAN[16] who evaluated the effect of α-tocopherol on serum cholesterol and lipoproteins in humans. A recent report showed that an oral 600 mg administration daily of dl-α-tocopheryl nicotinate caused the serum α-tocopherol level to increase to 25.2 μg/ml, whereas cases who received 400 mg daily of α-tocopheryl acetate showed an increase in serum level to 18.7 μg/ml[38]. On the other hand, it was reported that the administration of 600 IU daily of α-tocopheryl acetate for four weeks caused a 50～60% increase in the initial serum α-tocopherol level. However, this level returned to the initial one four days after the cessation of administration[22]. It was confirmed that 600 mg daily of α-tocopherol could raise the serum α-tocopherol level to more than twice the normal level, and that a loss of bile acids from the T-tube largely prevented an increase in the serum α-tocopherol level. However, further studies on the optimal dosages and schedules for α-tocopherol administration in humans are needed, to obtain more satisfactory clinical results.

Administration of α-tocopherol was found to be efficacious (ie. to improve the lithogenic index) in all cholesterol gallstone patients in Group I who received 600 mg daily, but was not efficacious in any of the Group II patients. Three patients with poor effect, who were given 600 mg of α-tocopherol daily, had cholesterol stones, however, in the one of these patients who had undertaken a total gastrectomy and in the other two young women patients, the T-tube had not been clamped before and throughout the study. For this reason serum α-tocopherol level in these three patients have not been raised adequately. In fact, in Case 6 it was 12.6 μg/ml, 7.80 μg/ml in Case 7, and thus it seemed that this was the reason why an improvement in the lithogenic index was not observed in these patients. On the other hand, two of seven patients in Group II had bilirubin stones. Gallstones are generally divided into four main types, that is, cholesterol stones, mixed stones, bilirubin stones, and black stones. MUKAIHARA reported that the chemical composition of bilirubin and black stones is different from that of cholesterol stones, and that the etiology of those stones might be different from that of cholesterol stones[27]. Furthermore, MARUYAMA reported that cholesterol-desaturated bile was obtained in patients with bilirubin or black stones, whose hepatic HMG-CoA reductase activity was low[23]. These findings suggest reasons for the lack of effect of α-tocopherol on biliary lipids in patients with bilirubin stones.

The pathogenesis of human cholesterol cholelithiasis has been ascribed to abnormal hepatic cholesterol metabolism. Of relevance to the etiology of gallstones, a decreased pool size of bile acids and some changes in biliary lipids, such as an increased hepatic secretion of cholesterol, decreased secretion of bile acids, and decreased secretion of phospholipids, have been noted in patients with cholesterol gallstones. The lithogenicity of hepatic and gallbladder bile has been

discussed in relation to the pathogenesis of cholesterol gallstones[6,36]. In previous studies of hamsters, the effect of α-tocopherol was observed to be stronger in the lithogenic diet-fed hamsters than in the chow-fed hamsters. The results (a decrease in biliary cholesterol level and an increase inprimary bile acids) suggested that α-tocopherol accelerates the activity of cholesterol 7α-hydroxy lase in the liver. In the present study, the findings were similar to those in hamsters, with increased hepatic HMG-CoA reductase activity being observed only in the patients with cholesterol stones, whose HMG-CoA reductase activity is usually activated[2,8], while cholesterol 7α-hydroxylase activity is suppressed[28,35].

In some patients with cholesterol stones, a diminution of the bile acid pool may be secondarily associated with a decreased output of phospholipids, which would further enhance lithogenesis. On the other hand, GRUNDY[14] showed that the most striking difference between young women with cholesterol gallstones and control subjects was the output of biliary cholesterol, and this difference contributed significantly to the greater lithogenicity of bile in the gallstone group, although the mechanisms for an increased secretion of cholesterol in bile have not been entirely elucidated. A recent report indicated that the triglyceride is transported as the major component of the VLDL, that the obligatory requirement of cholesterol as a component of the VLDL for transport of triglyceride, may be an important stimulation to the biosynthesis of cholesterol by the liver, and that the serum VLDL-triglyceride level closely correlated with hepatic HMG-CoA reductase activity[3,20]. From the result that α-tocopherol reduced serum VLDL-triglyceride level [34]. it was suggested that α-tocopherol suppressed its activity in the liver. SUGANO[40] indicated that the reduced HMG-CoA reductase activity induced an increased hepatic cholesterol 7α-hydroxylase activity. The decrease in biliary cholesterol and the increase in GCDCA or GCA might be secondarily caused by the reduced HMG-CoA reductase activity. It was suggested that α-tocopherol may be clinically useful for gallstone dissolution in combination with CDCA, and it is recommended for the prophylaxis of recurrence after a complete dissolution.

Acknowledgments

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和文抄録

ビタミンEの胆石形成予防効果に関する研究
(3) 臨床例における胆汁脂質に及ぼす影響に関する研究

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斎藤 徹

胆石症にてTチューブを挿入した臨床例に D-α-tocopherol カプセルを試作し，投与量と胆石の種類からその薬理学的効果に関する基礎的検討を行ない，以下の成績を得た．

1. 臨床の胆石症12例に手術後10日以上を経過し胆汁酸代謝が安定した時期に，10例には D-α-tocopherol を 600 mg，2例には 100 mg を1日量として経口投与し，Tチューブから得られる胆汁中脂質の濃度を測定した．

2. 胆汁中コレステロール濃度の低下と GCA 及び GCDCA 濃度の増加に基づく胆汁の催石指数の改善が認められたのは 600 mg 投与のコレステロール胆石症例であり，血清 α-tocopherol 濃度は 27～43 μg/ml と高値であった．

3. 一方，α-tocopherol の効果が認められなかった症例は，ビリルビン胆石の2例，胃全摘術後の1例，100 mg 投与の2例，およびTチューブのクランプを行なわなかった2例であり，その血清 α-tocopherol 濃度は 12.6 μg/ml と低値であった．

4. 全例 D-α-tocopherol カプセルに起因すると思わるれ副作用はなく，検査値異常も認めなかった．

以上の検討成績から，1日量として 600 mg の α-tocopherol の経口投与が臨床例においても胆汁の催石指数を改善させることが確認されたが，その効果が肝臓の cholesterol 7α-hydroxylase 活性が低下しているといわれるコレステロール胆石症例にのみ認められた事実から，α-tocopherol は肝臓にて本酵素活性に大きく関与していると推測された．