The Relationship between Cholelithiasis and Diabetes Mellitus : Discussion of Age, Obesity, Hyperlipidemia and Neuropathy

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TANNO, N., KOIZUMI, M. and GOTO, Y. *The Relationship between Cholelithiasis and Diabetes Mellitus : Discussion of Age, Obesity, Hyperlipidemia and Neuropathy.* Tohoku J. exp. Med., 1988, **154** (1), 11-20 — We investigated the patients who underwent operation for cholelithiasis and the diabetic patients at our clinic in order to determine whether there was a significant relationship between the occurrence of cholesterol gallbladder stone and age, obesity, hyperlipidemia, diabetes mellitus and neuropathy. In 647 patients undergoing surgery, cholesterol gallstones were not highly associated with diabetes mellitus or hyperlipidemia, compared with calcium bilirubinate and black stones. Eighty-seven percent of the male operated patients and 88% of the female patients were over 40 years old of age. Of the female patients in whom gallstones were detected at surgery, 36% were obese. We found cholesterol gallbladder stone in 11.5% (males 11%, females 12%) of 208 diabetic patients at our clinic. All of them were over 40 years old. The prevalence of cholesterol gallbladder stones was related to the decrease in motor nerve conduction velocity in the male diabetic patients ($p < 0.05$). We observed that method of treatment had no definite effect on the prevalence of gallbladder stones. Fifty-four percent of the diabetic patients was normolipidemic in both sexes. Obesity was present in 64% of the female cholesterol gallbladder stone patients. Our data suggest that age, obesity and poor contraction of the gallbladder could be high risk factors for cholesterol gallstone formation. ——— diabetes mellitus ; cholelithiasis ; motor conduction velocity ; hyperlipidemia

Diabetes mellitus has been thought to be frequently associated with cholelithiasis and inflammation of the biliary tract (Twiss and Carter 1952 ; Mundth 1962). But, the cause of gallstone complication in diabetes mellitus has not been completely clarified. It is known that the contraction of gallbladder is poor in diabetic patients, especially with autonomic neuropathy, compared with that of healthy subjects and is referred to as the diabetic neurogenic bladder (Gietelson 1963). On the other hand, hyperlipidemia and obesity may affect cholesterol saturation in bile. Obesity, hyperlipidemia and neuropathy are considered to be important factors in cholesterol gallstone formation. In the present study, we

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have first shown the incidence of obesity, hyperlipidemia and diabetes mellitus in patients undergoing surgery for gallstones. We discussed the complication of those items in cholesterol gallstone patients compared with that in calcium bilirubinate and black stone cases. Secondly, we have investigated the relationship among hyperlipidemia, neuropathy and cholesterol gallbladder stones in diabetic patients at our clinic.

MATERIALS AND METHODS

We studied 647 patients who underwent operation for cholelithiasis from 1978 to 1985 in the First Department of Surgery in Tohoku University and from 1984 to 1985 in the surgery division of Tohoku Rosai Hospital. They were comprised of 419 cholesterol gallstone cases (171 male cases), 106 calcium bilirubinate stone cases (54 male cases) and 122 black stone cases (55 male cases). In cholesterol gallstone cases, the prevalence of pure cholesterol, mixed, combination and combination plus mixed stones was 17%, 66%, 16% and 1%, respectively.

Furthermore, we investigated 212 cases of diabetes mellitus (116 male cases) in our clinic from 1981 to 1985. All of them received abdominal ultrasonography. Gallbladder stones were detected in 28 of 212 cases (13%), and no gallstones were found in except for the gallbladder. We classified gallbladder stones by criteria of Tsuchiya et al (Tsuchiya et al. 1986). Cases of cholesterol gallstones, black stones and calcium bilirubinate stones were twenty-four, three (2 male) and one (female), respectively. Only one female case (cholesterol gallstone) of them complained of abdominal pain, and another 27 cases were asymptomatic. Eventually, we studied 24 cholesterol gallbladder stone patients with diabetes mellitus (13 male cases) compared with 184 non-gallstone patients with diabetes mellitus (101 male cases). The relationship between age, sex, treatment and duration of diabetes mellitus, obesity, hyperlipidemia, neuropathy and cholesterol gallbladder stones were examined.

We estimated peripheral neuropathy by examination of motor nerve conduction velocity (MCV), sensory nerve conduction velocity (SCV) of the median nerve of the upper limb and achilles tendon reflex (ATR). We examined ATR on the knee of the patient while seated down of the bed. ATR, MCV and SCV were done in 158, 164 and 159 patients, respectively. Serum lipids were analyzed in an untreated state. We defined hyperlipidemia as serum triglyceride over 150 mg/100 ml and/or serum cholesterol over 250 mg/100 ml after an overnight fast. Obesity was defined to be when weight exceeded 120% of the ideal values.

The Student's *t*-test and χ^2 test were used in the statistical calculations.

RESULTS

Operated cases

Incidence of diabetes mellitus. Cholesterol gallstones were detected in 65% or 419 cases (171 male cases) of the 647 operated patients. Patients over 40 years old constituted 87% of the male and 88% of the female patients. The age distribution was similar in calcium bilirubinate and black stone cases (Table 1). The incidence of diabetes mellitus was 11% of the males and 8% of the females in cholesterol gallstone cases (Table 2). A similar proportion was found of the incidence in the males and the females in calcium bilirubinate and black stone cases. The presence of diabetes mellitus was not different between obese and

TABLE 1. *Operated cases from the First Department of Surgery at Tohoku University Hospital and the Surgery Division of Tohoku Rosai Hospital*

Age	Number of operated cases					
	Cholesterol stone		Calcium bilirubinate stone		Black stone	
	Male	Female	Male	Female	Male	Female
10~	0	1	0	0	0	2
20~	7	5	0	2	2	4
30~	16	25	1	1	5	4
40~	29	34	5	17	10	14
50~	64	82	17	6	19	14
60~	36	64	20	19	12	21
70~	16	33	10	9	7	8
80~	3	4	1	4	0	0
Total	171	248	54	52	55	67

TABLE 2. *Incidence of diabetes mellitus in the operated patients*

		Cholesterol stone		Calcium bilirubinate stone		Black stone	
		Male	Female	Male	Female	Male	Female
		(%)	(%)	(%)	(%)	(%)	(%)
Obesity	(+)	3/49 (6)	8/89 (9)	1/1 (100)	1/11 (9)	1/9 (11)	3/15 (20)
	(-)	16/122 (13)	13/159 (8)	8/53 (15)	2/41 (5)	4/46 (9)	2/52 (4)
Hyperlipidemia	(+)	4/55 (7)	8/80 (10)	1/18 (6)	1/14 (7)	1/18 (6)	2/12 (17)
	(-)	15/116 (13)	13/168 (8)	8/36 (22)	2/38 (5)	4/37 (11)	3/55 (5)
Total		19/171 (11)	21/248 (8)	9/54 (17)	3/52 (6)	5/55 (9)	5/67 (7)

Incidence is given in terms of number of DM cases/number of operated patients.

DM : diabetes mellitus.

non-obese patients (Table 2).

Obesity. Obesity was more prevalent in females than in males, in every gallstone group. The incidence of obesity was higher in cholesterol gallstone patients than in calcium bilirubinate and black stone cases in both sexes (Table 3).

Hyperlipidemia and diabetes mellitus. Hyperlipidemia was present in 32%

TABLE 3. *Incidence of obesity and hyperlipidemia in the patients who underwent surgery*

	Cholesterol stone		Calcium bilirubinate stone		Black stone	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Obesity(+)	49/171 (29)	89/248 (36)	1/54 (2)	11/52 (21)	9/55 (16)	15/67 (22)
Hyperlipidemia(+)	55/171 (32)	80/248 (32)	18/54 (33)	14/52 (27)	18/55 (33)	12/67 (18)

Incidence is given in terms of number of cases/total cases.

of cholesterol gallstone cases. The incidence of hyperlipidemia with cholesterol gallstones was not higher than that of calcium bilirubinate and black stones. Seventy to 80 percent of the patients were normolipidemic in every gallstone group (Table 3). In cholesterol gallstone cases with hyperlipidemia, hypertriglyceridemia was present in 55% (48 of 55 cases) of the males and 63% (50 of 80 cases) of the females (Table 4).

Location. Eighty-eight percent of the cholesterol gallstones were located in the gallbladder and 8% in both the gallbladder and common bile duct, 3% in common bile duct and 1% in intrahepatic bile duct. In calcium bilirubinate stones, there were 33% in common bile duct, 30% in intrahepatic bile duct, 20% in both gallbladder and common bile duct, 16% in gallbladder and 1% in both intrahepatic bile duct and common bile duct. In black stones, there were 92% in gallbladder, 4% in intrahepatic bile duct, 2% in common bile duct and 2% in both gallbladder and common bile duct. About 90% of cholesterol and black stones were located in gallbladder.

TABLE 4. *Serum lipids in the operated patients*

Serum lipid	Number of cases					
	Cholesterol stone		Calcium bilirubinate stone		Black stone	
	Male	Female	Male	Female	Male	Female
Hypercholesterolemia	2	18	3	4	2	3
Hypertriglyceridemia	48	50	13	8	14	7
Hypercholesterolemia + Hypertriglyceridemia	5	12	2	2	2	2
Normal	116	168	36	38	37	55
Total	171	248	54	52	55	67

Diabetic cases in our clinic

Incidence of gallbladder stones. In 212 diabetic patients at our clinic, gallbladder stones were found in 15 cases of the males and 13 cases of the females. Twenty four patients of them were cholesterol gallbladder stones. Cholesterol gallbladder stones were found in 11% of the males and 12% of the females and in the patients over 40 years old of age. There was no significant difference in the frequency of cholesterol gallbladder stones between the sexes (Table 5).

Considering three types of treatment, diet, oral agents and insulin treatment, the prevalence of gallbladder stones was 10, 15, 10% in the males and 13, 8, 13% in the females, respectively. There was no difference in frequency between the sexes among the three types of treatment (Table 6).

Obesity was frequently present in the females, 46% (43 of 94 cases), compared with the males, 18% (20 of 114 cases). Obesity was highly seen in cholesterol gallbladder stone group, 64% (7 of 11 cases), compared with non-gallbladder stone group, 43% (36 of 83 cases), in the females. The prevalence of cholesterol gallbladder stone was highly present in obese group, 16% (7 of 43 cases), compared with non-obese group, 8% (4 of 51 cases), in the females (Table 7).

TABLE 5. *Incidence of gallstone cases in diabetic patients from the Third Department of Internal Medicine at Tohoku University School of Medicine*

Age	Male (%)	Female (%)	Total (%)
10~	0/ 2 (0)	0/ 3 (0)	0/ 5 (0)
20~	0/ 2 (0)	0/ 5 (0)	0/ 7 (0)
30~	0/ 8 (0)	0/ 5 (0)	0/ 13 (0)
40~	0/ 16 (0)	3/13 (23)	3/ 29 (10)
50~	2/ 40 (5)	0/23 (0)	2/ 63 (3)
60~	7/ 35 (20)	3/29 (10)	10/ 64 (16)
70~	4/ 11 (36)	1/16 (6)	5/ 27 (19)
Total	13/114 (11)	11/94 (12)	24/208 (12)

Incidence of gallstone cases is given in terms of number of gallstone cases/number of diabetic patients.

TABLE 6. *Prevalence of cholesterol gallbladder stone in the diabetic patients divided into three types of treatment*

Method of treatment	Male (%)	Female (%)
Diet	5/50 (10)	6/46 (13)
Oral agents	5/33 (15)	2/24 (8)
Insulin	3/31 (10)	3/24 (13)

Values are given in terms of number of cases/total cases.

TABLE 7. *Incidence of obesity in the diabetic patients*

Sex	Cholesterol gallstone	Obesity	
		(+)	(-)
Males	(+)	2	11
	(-)	18	83
Females	(+)	7	4
	(-)	36	47

The prevalence of gallbladder stones in patients with the duration less than 10 years were 9% (7 of 77 cases) and 10% (6 of 61 cases) in males and females, respectively. With the longer duration more than 10 years, the incidence of cholesterol gallbladder stones increased to 16% (6 of 37 cases) in males and 15% (5 of 33 cases) in females.

Cholesterol gallbladder stones and neuropathy. There was no difference between gallbladder stone group and non-gallbladder stone group in ATR and SCV examination. Abnormally low values of MCV (under 50 m/sec) for the males in the cholesterol gallbladder stone group was seen more frequently (50%, 4 of 8 cases) than in the non-gallbladder stone group (19%, 15 of 79 cases) ($p < 0.05$). The prevalence of gallbladder stones was also significantly higher in the abnormal MCV group (21%, 4 of 19 cases) than in the normal MCV group (6%, 4 of 68 cases) ($p < 0.05$). There was however no difference among the females (Table 8).

Cholesterol gallbladder stones and hyperlipidemia. Hypercholesterolemia, hypertriglyceridemia, hypercholesterolemia with hypertriglyceridemia and normolipidemia were present in 6, 31, 9, 54% of the males and 16, 15, 15, 54% of the females, respectively. The corresponding prevalences of cholesterol gallbladder stones were 0, 17, 10, 10% in the males and 7, 7, 0, 18% in the females.

Hypertriglyceridemia was present in 46% (6 of 13 cases) in the male cholesterol gallbladder stone cases. But, 46% (6 of 13 cases) of the males and 82% (9

TABLE 8. *Abnormality of ATR, MCV and SCV in the diabetic patients*

Sex	Cholesterol gallstone	Number of cases					
		ATR		MCV		SCV	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Male	(+)	5	7	4	4	5	2
	(-)	42	31	64	15	57	26
Female	(+)	4	5	7	3	6	3
	(-)	28	36	50	17	42	18

ATR, achilles tendon reflet; MCV, motor nerve conduction velocity; SCV, sensory nerve conduction velocity.

TABLE 9. *Incidence of cholesterol gallstone cases in diabetic patients in relation to serum lipids*

Serum lipid	Male (%)	Female (%)	Total (%)
Hypercholesterolemia	0/ 7 (0)	1/15 (7)	1/ 22 (5)
Hypertriglyceridemia	6/ 35 (17)	1/14 (7)	7/ 49 (14)
Hypercholesterolemia + Hypertriglyceridemia	1/ 10 (10)	0/14 (0)	1/ 24 (4)
Normal	6/ 62 (10)	9/51 (18)	15/113 (13)
Total	13/114 (11)	11/94 (12)	24/208 (12)

Incidence is given in terms of number of cholesterol gallstone cases/number of diabetic patients.

of 11 cases) of the females were normolipidemic in cholesterol gallbladder stone patients (Table 9).

DISCUSSION

The incidence of gallstones associated with diabetes mellitus has been reported to be 20–30%. Feldman reported that gallstones were observed in 25% of diabetic patients and in 8% of non-diabetics in autopsy study (Marshall 1952; Feldman and Feldman 1954). Fukao et al. found gallstones in 3.9% of males and 5.4% of females in the mass screening for hepato-biliary diseases (Fukao et al. 1985). Onodera et al. reported in mass survey that gallstones were detected 2.1% of forties, 4.4% of fifties and 6.1% of over sixties, in males, and 3.7, 6.4, 10.3%, respectively, in females (Onodera et al. 1987). In the present study, we found gallbladder stone in 13% (28 of 212 cases) of diabetic patients. Cholesterol gallbladder stones were detected in 11.5% (24 of 208 cases), excluding one calcium bilirubinate stone and three black stone cases. Cholesterol gallbladder stones are considered to be highly associated (11.5%) with diabetic patients compared with the figures of their report about mass survey, because another kind of stones in addition of cholesterol gallstones could be included in reports of Fukao and Onodera et al.

First, we studied patients in whom cholesterol gallstones were detected in surgery in order to determine the correlation of gallstones with age, sex, obesity, hyperlipidemia and diabetes mellitus. At present, gallstones are mainly examined by ultrasonography. Over 90% of cholesterol gallstones are thought to be located in the gallbladder. In this series, 88–96% of the cholesterol gallstones were present in the gallbladder. However, surgical patients may reflect only a portion of cholesterol gallstone incidence, as many cases are thought to be silent. Therefore, we examined the diabetic patients by ultrasonography and investigated the relationship between neuropathy, hyperlipidemia and gallbladder stone.

It is pointed out that female gender, obesity, high calorie diet, age, American indian descent, terminal ileal disease, estrogen and clofibrate treatment may be

risk factors for cholesterol gallstones and most likely candidates are fair, fat, fertile women over forty years of age (Angel and Roncari 1978). We did not find a dominance of female gender. Obesity was however seen in a large percentage of the patients undergoing surgery for cholesterol gallstones, compared with those for calcium bilirubinate and black stones. Especially in the females, 36% of the operated cholesterol gallstone cases were obese. Obesity was present in 64% of the female cholesterol gallbladder stone patients with diabetes mellitus. With regard to age, all of the diabetic patients with gallbladder stones were over forty years old. In the operated patients with cholesterol gallstones, 87% of the males and 88% of the females were over forty years old of age.

The hepatic cholesterol secretion rate was enhanced with age but, inversely, bile acid synthesis decreased even in the healthy subjects. Consequently, cholesterol saturation of the bile increased (Einarsson et al. 1985). Thus, age is thought to be an important risk factor for cholesterol gallstones.

Onodera et al. reported that gallbladder contraction was poor in diabetic patients, compared with healthy subjects, and more poorly in the diabetics with autonomic neuropathy (Onodera et al. 1983). Goto (1985) pointed out that both peripheral and autonomic neuropathy could occur and progress simultaneously in diabetic patients. Moreover, a negative correlation between gallbladder contraction and MCV of the tibial nerve was recognized in diabetic patients without gallstones. Neither SCV nor ATR was not related to gallbladder contraction. So, we might expect a state of gallbladder contraction of diabetic patients by measuring a value of MCV. In the present study, we found that the prevalence of cholesterol gallbladder stones was related to the delay of MCV in the males. Namely, the occurrence of gallbladder stones was higher in the abnormal MCV group (21%) than in the normal MCV group (6%). Furthermore, abnormality of the MCV was observed in half of the gallbladder stone group.

The correlation between abnormality of MCV and the occurrence of cholesterol gallbladder stones was recognized in male diabetic patients. We can not explain why there was not a relationship like that in the females.

Our results suggest that abnormally low value of MCV is related to a poor contraction and bile stasis of gallbladder in diabetic patients.

Diabetes mellitus is commonly associated with abnormal lipid metabolism (Hayes 1972). In IDDM patients, chylomicron and very low density lipoprotein (VLDL) increase due to impaired lipoprotein lipase activity resulting from insulin deficiency and a decrease in apoprotein synthesis in liver, and hyperlipidemia types IV and V are observed. On the other hand, VLDL increases in NIDDM patients. Elevation of low density lipoprotein is also observed to be due to excessive intake of cholesterol and increase in cholesterol synthesis. Hyperlipidemia types II and IV are also present in NIDDM. Hyperlipidemia type IV has been reported to be frequently observed in diabetic patients (Kannel and McGee 1979; Simpson and Mann 1979). There is no agreement that hypercholes-

terolemia is generally associated with diabetes mellitus (Garcia and Mcnamara 1974 ; Howard et al. 1978). Analyzing serum lipoprotein of 294 patients without therapy in our diabetic clinic, the most common forms were types IIa, IIb, IV and V in that order, but half of the patients were normolipidemic. In this study, hypertriglyceridemia was encountered in 31% of the males and in 15% of the females, and hypercholesterolemia occurred in 6, 16%, respectively, in our diabetic clinic. But, 54% was normolipidemic in both sexes. Forty six percent of the male gallbladder stone cases showed hypertriglyceridemia, but, 82% of the female cases was normolipidemic. There was no tendency for a high association of hyperlipidemia with the cholesterol gallbladder stone group, compared with the non-gallbladder stone group. The prevalence of cholesterol gallbladder stones in the hyperlipidemic group was 13% (7 of 52 cases) and 5% (2 of 43 cases), in the males and females, respectively. The corresponding figures in normolipidemic group were 10% and 18%, respectively. There was no difference in the incidence of gallbladder stones between patients with and without hyperlipidemia. We did not observe that hyperlipidemia was closely related to cholesterol gallbladder stone formation in diabetics. In the operated patients, the occurrence of hyperlipidemia with cholesterol gallstones (32% in both sexes) was not different from that of calcium bilirubinate stones (32% of the males, 27% of the females) and black stones (33% of the males, 18% of the females).

Bennion et al. reported that bile was more saturated with cholesterol and was more favorable to cholesterol gallstone formation during insulin treatment than in the untreated diabetic state (Bennion and Grundy 1977). We divided the diabetic patients into three groups according to the method of therapy. But, we found no dominant prevalence of gallbladder stones in the insulin treated group compared with the diet and drug treated group.

Kajiyama et al. pointed that pure cholesterol stones were accompanied by hypertriglyceridemia and cholesterol supersaturated bile was seen in many cases of pure cholesterol stones (Kajiyama et al. 1982). They suggested that a disorder of not only biliary but also serum lipid metabolism seemed to be associated with the formation of pure cholesterol gallstones. Most of hyperlipidemia associated with diabetes mellitus reverts to normolipidemia easily with treatment. The relationship between serum and biliary lipid has not been fully investigated. Further study will be required concerning the relationship between lipid metabolism including of biliary lipid, neuropathy and gallbladder function in diabetic patients.

We investigated operated and diabetic patients. Age, obesity and abnormality of MCV were closely related to the prevalence of cholesterol gallbladder stone.

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