Impact of Food on Hepatic Clearance of Patients After Endoscopic Sphincterotomy

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Background: The recurrence rate of common bile duct stones (CBDS) is around 3–21% after treatment by endoscopic sphincterotomy (ES). Fatty meal has been shown to improve hepatic clearance in both patients with intact gallbladder and post-cholecystectomy after ES. This study tested the effects of different kinds of food on hepatic clearance by using quantitative cholescintigraphy (QC) in patients after ES.

Methods: Forty-seven patients after ES with abnormal QC were enrolled in our study. Complete ablation of sphincter function was confirmed by sphincter of Oddi manometry. Fasting QC was done in every patient shortly after normalization of liver function, and then followed with low-fat and fatty-meal QC. Each of the 47 subjects was observed for the effect on hepatic clearance at 3 different levels of treatments (diets and fasting). Additionally, possible factors responsible for recurrent CBDS were investigated by means of logistic regression.

Results: Both fatty and low-fat meals could significantly improve hepatic clearance compared with fasting in most patients after ES. But the response to food types was individualized. All patients tolerated the meals well. There was no significant relationship between the recurrence of CBDS and sex, age, intact gallbladder and presence of juxtapapillary diverticulum, CBD size, and improvement in hepatic clearance (≥ 5%) by food.

Conclusion: Both fatty and low-fat meals improved hepatic clearance in most of the patients with CBDS after ES, but the response to meals was individualized. Therefore, there is no need to restrict the amount of fat intake for patients who have undergone ES. [*J Chin Med Assoc* 2009;72(1):10–14]

Key Words: endoscopic sphincterotomy, food, hepatic clearance

Introduction

A large ultrasound-based study from Europe revealed that the overall rate of gallstone disease was 18.8% in women and 9.5% in men.[1] More than 20 million people have gallbladder disease in the United States.[2] The introduction of endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy (ES) in the 1970s has virtually supplanted surgery for the treatment of common bile duct stones (CBDS).[2,3] However, the recurrence rate of CBDS is around 3–21% after ES and as high as 80% after the first recurrence.[4–10] Gallbladder left *in situ* and large bile duct size (≥15 mm) are associated with the relapse of biliary symptoms in patients after ES, while bile duct size and a large juxtapapillary diverticulum (JPD) are associated with recurrent bile duct stones (RBDS).[11,12] However, elective cholecystectomy after ES does not significantly reduce the incidence of recurrent biliary complications and is not always necessary.[13,14] Large bile duct and JPD may result in bile stasis or impairment of hepatic clearance.[15,16] Delayed biliary emptying or hepatic clearance occurred commonly in patients with a history of choledocholithiasis, even after complete ES.[12,17]

Quantitative cholescintigraphy (QC) is an ideal non-invasive test for evaluating hepatic clearance and predicting the occurrence of RBDS,[18–21] but there is still no effective method for preventing this complication.

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Some drugs such as ursodeoxycholic acid and aspirin have been employed to prevent gallstone formation in patients on a very low-calorie diet, but their effects on RBDS are unknown.[22–24] Fatty meal has been shown to reduce the risk of cholecystectomy and also to improve hepatic clearance in patients with intact gallbladder and post-cholecystectomy after ES.[25,26] It is questionable as to whether or not other kinds of food have a similar impact on hepatic clearance. In the present study, we compared the effects of fatty and low-fat meals on QC in patients with abnormal hepatic clearance after ES and tested the possible factors affecting the recurrence of CBDS.

Methods

Between April 1999 and October 2003, 139 patients with choledocholithiasis after ES and complete biliary clearance received QC to evaluate their hepatic clearance after normalization of liver function. Forty-seven patients with abnormal QC (45-minute clearance of radioisotope < 57%) were enrolled in our study. Complete ablation of sphincter function in these 47 patients was confirmed by sphincter of Oddi manometry. Sphincter of Oddi manometry was performed as previously described,[16] and the complete ablation of sphincter function was defined as wide opening of the papilla and the basal pressure of the sphincter being < 10 mmHg.

Fasting (routine) QC was performed following intravenous administration of 8 mCi (296 MBq) of technetium-99m disofenin (Hepatolite; CIS-US, Bedford, MA, USA) to patients after overnight fasting. Imaging was carried out using a large-field gamma camera with low energy, all-purpose collimator (Siemens Orbiter 75, Chicago, IL, USA) connected to a computer (Microdelta, Chicago, IL, USA). Data were recorded with patients in supine position under the gamma camera. A continuous series of 60 frames of 1-minute duration each was stored on the computer disk for later analysis. Static views at 1, 2, 4 and 6 hours were also recorded. A rectangular region of interest was identified and outlined over the right hepatic lobe, and a time-activity curve was created. The time to reach maximal count (T_{max}), half time for hepatic clearance from T_{max} ($T_{1/2}$) and hepatic clearance percentage of the maximal counts at 45 minutes and 60 minutes (E45′, E60′) were calculated for comparison. The reference values of positive limit were T_{max} = 13 minutes; $T_{1/2}$ = 30 minutes; E45′ = 57%; and E60′ = 72%.[20]

The mean time lag between low-fat meal QC performed after fasting QC was 1.4 ± 0.9 months and between fatty and low-fat meal QC was 1.5 ± 1.4 months. The low-fat meal consisted of 2 pieces of toast, 250 mL of low-fat milk and 250 mL of fruit juice (fat, 0.3 g; protein, 13 g; carbohydrate, 77 g; total, 363 kcal), while the fatty meal consisted of 2 fried eggs, 250 mL of full-fat milk and 250 mL of fruit juice (fat, 28 g; protein, 22 g; carbohydrate, 12 g; total, 388 kcal). Meals were taken 30 minutes before isotope injection and the rest of the procedure was the same as for fasting QC.

The Department of Medical Research and Education of Kaohsiung Veterans General Hospital approved this study, and informed consent was obtained from each patient.

This was a repeated measures study with a balanced design in which each of the 47 subjects was observed at 3 different levels of treatments, namely: fasting (treatment 1); low-fat meal (treatment 2); and fatty meal (treatment 3). General linear model of ANOVA was used to test the differences in hepatic clearance among the 3 levels of the factor (diet), and Tukey's honestly significant difference (HSD) was used as a multiple comparison test. Furthermore, the possible factors (age, sex, CBD diameter, intact gallbladder, presence of juxtapapillary diverticulum, improvement in hepatic clearance ≥ 5% at 45 minutes or 60 minutes after meals) affecting the recurrence of CBDS were analyzed by logistic regression. A p value of < 0.05 was considered to be significant.

Results

Patients' characteristics are shown in Table 1. The mean age of all the patients was 67 ± 11 years; 32 patients (68%) were male. Twenty-two patients (47%) had JPD, and 21 patients (44.7%) had an intact gallbladder. Twenty-seven (57%) patients had bile duct size ≥ 15 mm. There was no significant difference in fasting E45′ with regard to the differences in sex, age, gallbladder status, presence of JPD and bile duct size (Table 2). The mean follow-up period was 62 ± 34

Table 1. Patients' characteristics

	Patients	
	n	%
Male/female	32/15	68/32
Age > 65 yr *vs.* ≤ 65 yr	28/19	60/40
Juxtapapillary diverticulum (yes/no)	22/25	47/53
Intact gallbladder (yes/no)	21/26	45/55
Bile duct size ≥ 15 mm *vs.* < 15 mm	27/20	57/43
Recurrent bile duct stones (yes/no)	12/35	26/74

months, and the mean recurrence period of CBDS was 23 ± 13 months.

The QC results are shown in Table 3. The effect of the diets on hepatic clearance was highly significant ($p < 0.001$), as shown by ANOVA. Tukey's HSD test further indicated that there were significant improvements in hepatic clearance with the fatty meal (treatment 3) compared to fasting (treatment 1), as well as with the low-fat meal (treatment 2) compared to fasting (treatment 1), but not between the low-fat and fatty meals (treatments 2 and 3).

The individual responses to fatty or low-fat meal revealed by improvement in radioisotope elimination ≥ 5% at 45 or 60 minutes when compared with fasting QC is shown in Table 4. Although most of the patients showed a positive response to both types of meals, some demonstrated a contradictory result. Twelve patients (26%) developed RBDS during the follow-up period. Factors including age, sex, bile duct size, intact gallbladder, presence of JPD, and the influence of meals on QC did not significantly affect the recurrence of CBDS (Table 5). All patients tolerated the meals well.

Table 2. Possible factors affecting the fasting E45′ value

	Patients (*n*)	E45′ (%)*	*p*
Gender			0.67
Male	32	29 ± 11	
Female	15	27 ± 11	
Age (yr)			0.48
> 65	28	27 ± 12	
≤ 65	19	30 ± 11	
Juxtapapillary diverticulum			0.41
Yes	22	30 ± 12	
No	25	27 ± 11	
Intact gallbladder			0.17
Yes	21	26 ± 11	
No	26	30 ± 11	
Bile duct size (mm)			0.69
≥ 15	27	29 ± 12	
< 15	20	27 ± 11	

**Data presented as mean ± standard deviation.*

Table 3. Results of quantitative cholescintigraphy in 47 patients after endoscopic sphincterotomy

	Fasting	Low-fat meal	Fatty meal
T_{max} (min)	$20 \pm 7^{a,b}$	$15 \pm 5^{a,c}$	$14 \pm 5^{b,c}$
$T_{1/2}$ (min)	$53 \pm 22^{d,e}$	$40 \pm 10^{d,f}$	$37 \pm 10^{e,f}$
E45′ (%)	$28 \pm 11^{g,h}$	$41 \pm 12^{g,i}$	$45 \pm 12^{h,i}$
E60′ (%)	$43 \pm 13^{j,k}$	$54 \pm 10^{j,l}$	$58 \pm 10^{k,l}$

$^{a,b,d,e,g,h,j,k}p < 0.001$; $^{c,f,i,l}p > 0.05$. T_{max} = time to reach maximal radioactivity; $T_{1/2}$ = time for decrease from peak to 1/2 maximal radioactivity; E45′ and E60′ = percent of maximal radioactivity excreted at 45 and 60 minutes.

Discussion

QC is a noninvasive test to evaluate hepatic clearance and biliary emptying.[22,27] We chose the region of interest over the right lobe of the liver to avoid higher background activity over the left liver and bile duct.[28,29] The slopes for disappearance of isotope from the region of the right liver, hilum, and CBD were virtually identical; hepatic clearance in the right liver is therefore

Table 4. Individual response to fatty meal or low-fat meal shown by quantitative cholescintigraphy

Response to	Meal	Patients (*n*)
Fatty meal (+)*	Low-fat meal (+)	36
Fatty meal (+)	Low-fat meal (–)[†]	5
Fatty meal (–)	Low-fat meal (+)	2
Fatty meal (–)	Low-fat meal (–)	4

**Increase in radioisotope elimination ≥ 5% at 45 or 60 minutes compared with fasting quantitative cholescintigraphy; [†]increase in radioisotope elimination < 5% or decrease in radioisotope elimination at 45 or 60 minutes compared with fasting quantitative cholescintigraphy.*

Table 5. Possible factors affecting recurrent bile duct stones as analyzed by logistic regression

Factors	Recurrence *vs.* no recurrence	OR	95% CI	*p*
Sex (male *vs.* female)	8/32 *vs.* 4/15	0.92	0.23–3.70	0.90
Age > 65 yr *vs.* ≤ 65 yr	5/28 *vs.* 7/19	0.37	0.10–1.43	0.15
CBD diameter ≥ 1.5 cm *vs.* < 0.5 cm	8/27 *vs.* 4/20	1.68	0.43–6.64	0.46
Intact gallbladder (yes *vs.* no)	6/21 *vs.* 6/26	1.33	0.36–4.97	0.67
Juxtapapillary diverticulum (yes *vs.* no)	4/22 *vs.* 8/25	0.47	0.12–1.86	0.28
Response to fatty meal (yes *vs.* no)	10/2 *vs.* 31/4	0.65	0.10–4.07	0.64
Response to low-fat meal (yes *vs.* no)	11/1 *vs.* 27/8	3.26	0.36–29.2	0.29

OR = odds ratio; CI = confidence interval; CBD = common bile duct.

comparable to biliary emptying of the CBD in the absence of biliary obstruction and parenchymal liver disease.[20,27] It has been shown that in asymptomatic control patients, more than half of the radioisotope was excreted at 45 minutes after administration.[20] However, QC is not sensitive enough to detect the difference between organic and functional disorders of the biliary tract, especially in patients with a dilated bile duct.[21] In this study group, the possible organic obstruction of the bile duct could be excluded by normalization of liver function before QC and low sphincteric basal pressure by sphincter of Oddi manometry. However, even in the patient who receives complete ES, bile secreted from the liver may be diverted to the gallbladder or through the bile duct into the duodenum, depending on the resistance to the bile flow. This depends on the contraction state of the gallbladder as well as the pressure gradient of the sphincter of Oddi during duodenal contraction. Following ingestion of a meal, the gallbladder contracts actively and empties the bile. The process is primarily mediated by the release of cholecystokinin (CCK) since it can be completely blocked by the administration of a CCK antagonist.[30] The effect on bile flow by the gallbladder in contrast to patients without a gallbladder could be minimized by the administration of artificial CCK or synthetic fatty meal.[31] We used natural fatty food instead of artificial products or drugs for the study of hepatic clearance with the same effect on gallbladder, and it was more physiological and cheaper.[26]

Intact sphincter of Oddi is a passive resistor to control the passage of bile flow into the duodenum. Therefore, bile should pass freely into the duodenum after ES. In this group of patients under investigation, all had persistent impairment of hepatic clearance (E45′) even after ES, which was a risk factor for RBDS.[19] Theoretically, normalization of hepatic clearance may minimize the episodes of recurrent bile duct symptoms, but no safe and effective medicine or method is helpful up to now. Although frequent nut consumption may reduce the risk of cholecystectomy for gallstone disease in women, further adjustment of fat consumption did not materially alter the relation.[26] We therefore tested the response of patients by using different types of diets compared to fasting in terms of hepatic clearance. We found that there were significant improvements in all the parameters of hepatic clearance if patients were pretreated by fatty and low-fat meals compared to fasting. But there was no significant difference between the patients pretreated by fatty versus low-fat meals. However, the response of hepatic clearance to meals was individualized. Although there was no direct correlation between responsiveness to fatty or low-fat meals and RBDS in this study, the improvement in hepatic clearance was probably via increase of bile flow after meals, which helps to flush the bile duct and clear the particles or sandy stones.

The drawbacks of this study were small sample size and the lack of a standard diet being suggested after ES. Although we could not figure out the clinical importance of different meals in the prevention of biliary complications, our study suggests that fat restriction or prolonged fasting may be inappropriate for patients with CBDS who have received ES. Further studies are needed to explore the influence of frequency and types of food intake on hepatic clearance and RBDS.

In conclusion, both fatty and low-fat meals improved hepatic clearance in most of the patients after ES and the response was individualized. Therefore, it is possible to benefit patients in terms of reducing the risk of RBDS if the eating habit is changed to frequent small amounts of food instead of prolonged fasting and fat restriction.

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