Gallbladder Function in Diabetic Patients

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Gallbladder emptying and filling was studied in eight diabetic and six normal control patients. None of the patients had gallstones. Cholescintigraphy was performed using [^{99m}Tc]disofenin, and gallbladder emptying was studied using a 45-min i.v. infusion of the octapeptide of cholecystokinin (OP-CCK) 20 ng/kg · hr. The peak filling rate was greater in diabetic than in normal subjects; however, emptying of the gallbladder in response to OP-CCK was significantly less in the diabetic subjects (51.6 ± 10.4% compared with 77.2 ± 4.9%). When the diabetic group was subdivided into obese and nonobese diabetics, the obese diabetics had a much lower percentage of emptying than the nonobese diabetics (30.0 ± 10.4% compared with 73.1 ± 9.3%). These findings suggest that obese diabetics may have impaired emptying of the gallbladder even in the absence of gallstones. The more rapid rate of gallbladder filling in obesity may indicate hypotonicity of the gallbladder. The combination of these abnormalities may predispose the obese diabetic to the development of gallstones.

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We have recently reported a method for studying filling and emptying of the gallbladder using cholescintigraphy (*1*). Emptying of the gallbladder was found to be maximal with a 45-min constant i.v. infusion of the octapeptide of cholecystokinin (OP-CCK) (*1*). In the present study we have used this method to evaluate the function of the gallbladder in a group of diabetic patients without gallstones. Diabetic patients were selected because diabetes frequently has been cited as a risk factor for the development of gallstones (*2–6*). Since dysfunction of the gallbladder may result in bile stasis and lead to the formation of gallstones, it seemed reasonable to study gallbladder function in patients at risk for the development of gallstones.

MATERIALS AND METHODS

This study was approved on January 19, 1982, by the Research and Development Committee and the Human Rights Committee of the Oakland Veterans Administration Medical Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; informed consent was obtained from all patients.

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Control Subjects

Control subjects were selected from the GI outpatient clinic of the Oakland VA Medical Center. All patients had normal liver function tests and no evidence of gallstones by oral cholecystography or sonography of the gallbladder. All six control patients were male with a mean body weight of 81.7 kg. Half of the control patients were obese as defined by a weight in excess of 10% of their ideal body weight, according to the Metropolitan Life Insurance Company, Health and Safety Education Division, 1983 (Table 1).

Diabetic Subjects

The eight male diabetic subjects had a mean body weight of 87 kg. Half of the eight diabetics were obese as defined above. Five diabetics had had their disease for more than 10 yr; the other three had had their disease for 2, 6, and 9 yr, respectively. Three were insulin-dependent, while the other five had never received insulin. None had gallstones as determined by either oral cholecystography or sonography of the gallbladder. None of the patients had orthostatic hypotension. Evidence for peripheral neuropathy was found in only two of five patients studied by measurements of nerve conduction velocities. Glycosylated hemoglobin was elevated in four of five patients studied.

TABLE 1
Gallbladder Function in All Study Patients

Patients	Age (yr)	Ht (in.)	Ideal body wt. (lb)	Actual body wt. (lb)	Gallbladder ejection fraction (%) at 45 min	Peak filling rate (%/min)	Time to peak filling rate (min)	Time of maximum counts (min)
Controls								
1	50	71	166	164	75.4	4.4	27	70
2	57	72	170	201	73.5*	6.5	35	54
3	51	77	187	220	96.4*	6.0	31	55
4	58	70	166	195	66.5*	10.4	37	55
5	57	66	151	152	85.8	4.6	13	84
6	65	71	184	182	65.4	4.4	32	70
				Mean ± s.e.e.	77.2 ± 4.9	6.1 ± 0.9	29.2 ± 3.5	64.7 ± 4.9
Diabetics								
1	64	61	174	165	96.5	8.3	22	44
2	61	68	157	175	13.9*	8.5	49	74
3	63	69	163	168	51.5	5.8	27	47
4	60	70	166	210	28.7*	9.4	22	50
5	65	71	166	170	68.7	6.9	22	85
6	63	69	160	171	75.8	5.7	40	80
7	62	65	148	204	17.7*	13.6	11	80
8	41	72	170	271	59.7*	—	—	—
				Mean ± s.e.e.	51.6 ± 10.4	8.3 ± 1.0	27.6 ± 4.8	65.7 ± 6.8

* Obese, as defined in text. All controls and diabetics were men.

Cholescintigraphy

The methods for measuring filling and emptying of the gallbladder have been previously described (*1*). Briefly, a gamma camera interfaced with a computer was used to obtain images of the liver and gallbladder at a frame rate of 1 frame/min. All patients were in the fasting state and were injected intravenously with 0.5-1.0 mCi [^{99m}Tc]disofenin. The filling phase of the gallbladder was studied using a parallel hole collimator, and the emptying phase was studied with a pinhole collimator. The filling phase was started shortly after injection of the radionuclide, and was continued for at least 60 min. Emptying of the gallbladder was stimulated by a constant i.v. infusion of OP-CCK 20 ng/kg · hr over 45–60 min administered by IVAC infusion apparatus. The emptying phase was started 60–90 min after injection of radionuclide.

Analysis of the filling and emptying phases of the gallbladder was performed by defining regions of interest over the gallbladder and subtracting background activity over the region of liver. Time-activity curves were generated for the filling and emptying phases. The emptying curves were normalized to 10^3 counts at time 0 (time at which OP-CCK was started). The activity at timed intervals of 15, 30, 45, and 60 min were corrected for the physical decay of injected isotope. The percentage of gallbladder emptying was calculated using the following formula:

$$\frac{\text{(Initial counts in gallbladder)} - \text{(Final Counts in gallbladder)} \times 100}{\text{Initial counts in gallbladder}}$$

The following parameters were examined for the filling phase of the gallbladder: (a) peak filling rate, which is defined as the maximum increase in counts from minute to minute, expressed as a percentage of maximum counts per min; (b) the time to peak filling rate; and (c) the time to attainment of maximum number of counts over the gallbladder region.

Statistical Analysis

The statistical difference between the groups was analyzed using Student's t-test for unpaired values. p-values >0.05 were considered not significant.

RESULTS

Table 1 shows the age, height, weight, and parameters of gallbladder function in all the study patients. The mean ejection fraction of the gallbladder at 45 min after starting OP-CCK was 77.2 ± 4.9% in controls and 51.6 ± 10.4% in diabetics ($p < 0.05$). Figure 1 shows that the group of diabetic patients had significantly less emptying at all three time intervals evaluated as compared to the normal subjects ($p < 0.05$).

When normal and diabetic groups were subdivided

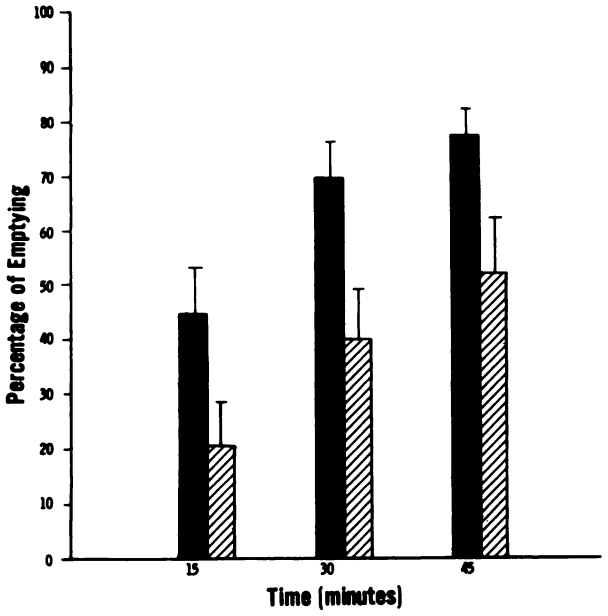

FIGURE 1
Percentage of emptying of gallbladder at various times after constant i.v. infusion of OP-CCK in diabetic and control groups. Means ± s.e.e.s are shown. Differences are significant at all times measured. (■) Control-constant infusion of 20 ng/kg-hr (*6*); (▨) Diabetic-constant infusion of 20 ng/kg-hr (*8*)

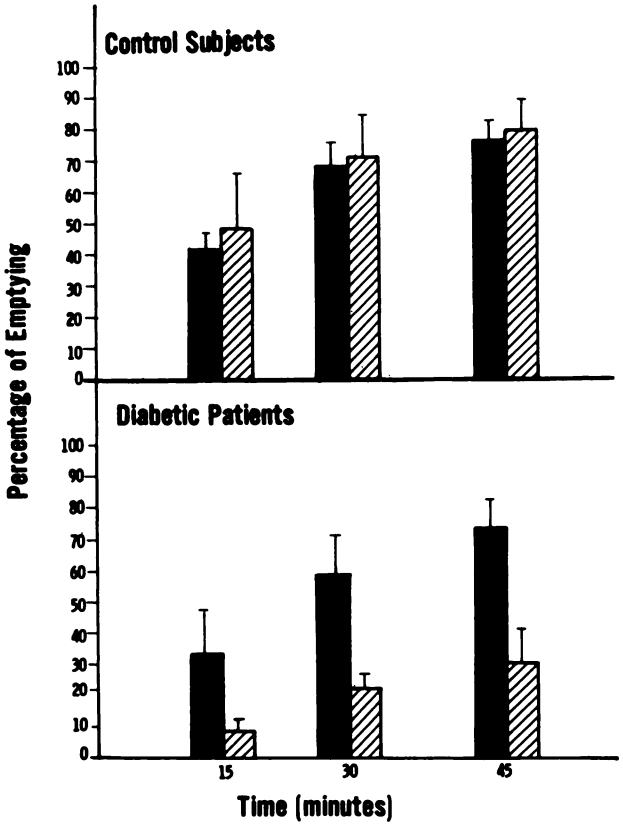

FIGURE 2
Percentage of emptying of gallbladder at various times after OP-CCK in same patients as in Fig. 1, but after subdividing each group into obese and nonobese subgroups. Means ± s.e.e.s are shown. There was no significant difference between obese (▨) and nonobese (■) controls, but obese diabetics had less emptying than nonobese diabetics

into obese and nonobese groups, no difference in the percentage of gallbladder emptying was found between the obese and nonobese normal subjects (Fig. 2). However, the four obese diabetics had significantly less emptying than the four nonobese diabetics (Fig. 2) at 30 and 45 min ($p < 0.025$). At 45 min the mean ejection fraction was 30.0 ± 10.4% in obese diabetics and 73.1 ± 9.3% in nonobese diabetics. Three of the four obese diabetic subjects were insulin-dependent.

No correlation was found between gallbladder emptying and serum glucose, glycosylated hemoglobin, or the duration of diabetes. Of the two patients with abnormal nerve conduction velocities, one had normal and one had abnormal emptying of the gallbladder at 45 min.

The diabetic subjects had a higher mean peak filling rate (Table 1) compared with the normal subjects (8.3 ± 1.0%/min compared with 6.1 ± 0.9%/min, respectively) but the difference was not statistically significant ($p < 0.10$). However, the difference between obese diabetics and either controls or nonobese diabetics was significant ($p < 0.025$ and $p < 0.05$, respectively). Interestingly, the obese controls also had higher filling rates than the nonobese controls (7.6%/min compared with 4.5%/min, $p < 0.05$). The other parameters of gallbladder filling (time to peak filling rate and time to maximum counts) were not different between control and diabetic subjects (29.2 min compared with 27.6 min, and 64.7 min compared with 65.7 min, respectively).

DISCUSSION

Our previous work has shown that a constant i.v. infusion of OP-CCK 20 ng/kg · hr was sufficient to induce maximal contraction of the normal gallbladder within 45 min (*1*). Doubling the dose or prolonging the rate of infusion did not cause greater contraction (*1*).

We have used this technique to show that a group of diabetic subjects had decreased emptying of the gallbladder in response to OP-CCK as compared with normal subjects. However, when the diabetic group was subdivided into obese and nonobese groups, it was noted that obese diabetics had significantly less emptying than did the nonobese diabetics. Since obesity per se could be associated with decreased contractility of the gallbladder, we compared obese nondiabetic subjects with their nonobese normal controls and found no significant difference in their response to OP-CCK. Also, the mean ejection fraction of the nonobese diabetics was not significantly different from that of the controls

(73.1% compared with 77.2%, respectively). Therefore, it would appear that the gallbladders of obese diabetic subjects, but not obese nondiabetic subjects, may have impaired emptying. It is of interest that three of the four obese diabetics were also insulin-dependent. It is well known that both obesity and insulin therapy are associated with a high cholesterol content of bile, thus predisposing to gallstones (*7–10*).

There is evidence to suggest that gallstones may be associated with decreased emptying of the gallbladder (*11*). None of our patients, diabetic or otherwise, had gallstones. We suggest that the impaired contractility of the gallbladder in some diabetic patients may predispose to the subsequent development of gallstones. Long-term studies of diabetics without gallstones, but with abnormal emptying of the gallbladder, would have to be carried out to determine whether stones would eventually develop in these patients.

In our studies of the filling phase of the gallbladder, we found only one possible abnormality in obese diabetics and obese controls. They seemed to have a higher peak filling rate than did the nonobese diabetics and controls. The time required to achieve the peak filling rate and the time of maximal filling clearly were normal. These findings could be explained by an increased compliance or hypotonicity of the gallbladder, which could lead to dilation of the gallbladder (*12*). Hypotonicity could also account for the reduced emptying response to OP-CCK. The combined effects of poor emptying and possibly increased filling rate and volume could lead to bile stasis within the gallbladder and the formation of stones. Our inability to measure the absolute volume of the gallbladder by cholescintigraphy did not permit us to determine whether gallbladder volumes were different between diabetics and normal subjects.

In conclusion, although the number of diabetic subjects studied so far is small, the marked differences in gallbladder emptying between obese diabetic subjects and all others we have studied warrant these preliminary conclusions. We have shown (a) the usefulness of a constant infusion of OP-CCK to study the contractility of the gallbladder in normal and diabetic subjects; (b) obese and/or insulin-dependent diabetics may have impaired emptying of the gallbladder; (c) diminished emptying of the gallbladder can occur without demonstrative gallstones and therefore may precede or predispose the diabetic to the development of gallstones; and (d) obesity per se may be associated with increased compliance of the gallbladder.

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