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Gallbladder Dysfunction in Diabetes Mellitus

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To further elucidate the mechanism of impaired gallbladder emptying in diabetics with and without neuropathy, gallbladder function was assessed by ultrasonography following a medium-chain triglyceride (lipomul, 1.5 mg/kg) infusion into the duodenum and compared to that during intravenous infusion of cholecystokinin in diabetic women. Results were compared with five healthy control women. Mean (±SD) maximal percent gallbladder volume in diabetics following lipomul was reduced to 49 ± 8% and after intravenous cholecystokinin to 47 ± 9%, which was less than those in controls, 21 ± 9% and 24 ± 6%, respectively, but not significantly different. Further analysis of gallbladder emptying to lipomul differentiated two subgroups of diabetics: one subgroup (N = 5) had emptying comparable to controls (responders), while the other (N = 5) had very modest emptying (nonresponders). Two of the patients in the latter group had normal gallbladder emptying during exogenous cholecystokinin and their response would be compatible with visceral neuropathy. Blood levels of cholecystokinin, measured by bioassay, following lipomul and exogenous cholecystokinin were similar in controls and diabetics. Presence of diabetic neuropathy did not correlate with impaired gallbladder emptying. Follow up at 6 and 12 months of the three nonresponder diabetics revealed that no gallstones had developed and that two of them became responders to exogenous cholecystokinin. We conclude that: (1) following lipomul, about 50% of diabetics in this study have impaired gallbladder emptying, which is not strictly correlated with diabetic neuropathy; (2) this was not due to abnormal cholecystokinin release; (3) in diabetic patients with impaired gallbladder emptying another abnormality may be present in the gallbladder; and (4) impaired gallbladder contraction may not lead to gallstone formation in one-year follow-up.

KEY WORDS: gallbladder; ultrasound; diabetes mellitus; cholecystokinin; neuropathy.

Previous studies in patients with diabetes mellitus have described an increased incidence of gallstones (1), supersaturated bile (2), and a larger and poorly contracting gallbladder (3–5). Impaired gallbladder emptying could be the earliest abnormality. The mechanism of the gallbladder emptying abnormality in diabetics is not completely understood, although it has been proposed that it could represent a manifestation of denervation caused by visceral neuropathy (2–5). Diabetic autonomic neuropathy affecting the gastrointestinal tract has been well described and appears to cause gastroparesis, diarrhea, dysphagia, motility abnormalities in the small bowel, and in the colon with constipation, and rectal sphincter hypotonia (6–9). Abnormal gallbladder

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contraction in diabetics with autonomic neuropathy is referred to as diabetic neurogenic gallbladder (5, 8, 10, 11). However, it could also be determined by humoral mechanisms, since a close correlation between contraction of the gallbladder and postprandial circulating blood levels of cholecystokinin (CCK) or administration of exogenous cholecystokinin has been shown (12–16). Furthermore, cholecystokinin receptors on gallbladder smooth muscle have been characterized and fewer receptors have been described in patients with poor gallbladder contraction (17). The possibility that impaired gallbladder contraction in diabetics could be related to (1) lesser CCK release from the small intestine, (2) impairment of gallbladder smooth muscle contractility, and (3) decreased CCK receptors on the gallbladder smooth muscle of diabetics have not been investigated.

The purpose of this study was twofold: (1) to determine whether diabetics with and without visceral neuropathy have a different response to endogenous versus exogenous CCK release and (2) to determine whether diabetics have abnormal postprandial CCK release.

MATERIALS AND METHODS

Subjects. Female diabetic subjects (N = 10) were randomly recruited for the study from the outpatient diabetic clinic. Both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients were included. We chose to investigate only female subjects since there are significant differences in gallbladder volume and emptying between males and females (18). Patients with severe anemia (Hb < 10 g), renal disease (serum creatinine >1.5 mg/dl), endocrine disease (thyroid, adrenal, or parathyroid abnormalities), heart disease (CHF, angina, or history of arrhythmias), and a previous history of gastrointestinal complications such as severe constipation, persistent diarrhea or gastroparesis, gallbladder disease, cholecystectomy, or gallstones as determined by baseline screening ultrasonography were excluded from the study. Five healthy female volunteers without a family history of diabetes served as controls. Following the approval of the protocol by the Investigational Review Board of the Los Angeles County+University of Southern California Medical Center, an informed consent was obtained. All subjects had a complete physical and detailed neurological examination. Diabetic peripheral neuropathy was assessed by a detailed questionnaire related to the degree of symptoms using a visual analog scale, a thermal sensitivity tester (19), and an Optacon Tactile Sensor for peripheral neuropathy (20). Diabetic autonomic neuropathy was assessed by a detailed questionnaire related to severity of autonomic symptoms using a scale of 0–10, R-R variation using a single-lead ECG tracing (21), and measurement of supine and standing blood pressure.

Study Design. Subjects were admitted to the Clinical Research Center (CRC) for two consecutive days. On day 1, after an overnight fast (12 hr), a single-lumen radiopaque nasoduodenal tube (3 mm OD) with a small weighted tip was swallowed and positioned intraduodenally 3–5 cm beyond the pylorus under fluoroscopic guidance. An indwelling 21-gauge butterfly catheter was placed in the antecubital fossa and blood was obtained for fasting glucose. In the diabetics, insulin or the oral hypoglycemic agent was withheld. Subjects were taken to the ultrasonography (US) laboratory where they rested comfortably in the supine position and the gallbladder was identified. Each subject then received an infusion of 1.5 mg/kg of lipomul, 71% fat/weight medium-chain triglyceride (Upjohn, Kalamazoo, Michigan) (22), over 20 min through the duodenal tube. Blood samples were withdrawn before the lipomul (at baseline) and at 15, 30, 45, 60, and 90 min after the beginning of the infusion. Samples were collected on iced EDTA-containing tubes and immediately centrifuged, and the plasma was stored at −20°C until analyzed. Gallbladder images by US were obtained at baseline (fasting) and sequentially at 15, 30, 45, 60, and 90 min after the beginning of the lipomul infusion. At the completion of the first-day protocol, which lasted 90 min, the nasoduodenal tube was removed, the patients were returned to the CRC, and the diabetic patients were given insulin or oral hypoglycemic agent in addition to an American Diabetes Association (ADA) meal.

On day 2, after an overnight fast (12 hr), an intravenous line was placed in the antecubital vein. The subjects were transported to the ultrasonography laboratory. An infusion of 30 ng/kg/hr (equivalent to 26.2 pmol/kg/hr) of the cholecystokinin analog CCK-8 (Kinevac, E.R. Squibb & Sons, Inc., Princeton, New Jersey) was diluted in 154 mM NaCl and infused intravenously by use of a Harvard pump (Harvard Apparatus Co., Inc., South Natick, Massachusetts), at a rate of 1 ml/min for 20 min. Blood was collected before and during the infusion through another indwelling butterfly catheter in the opposite antecubital vein. Blood samples were drawn at baseline and at 15, 30, 45, 60, and 90 min after the beginning of the infusion and processed as on day 1. Gallbladder images by ultrasound were obtained at baseline (fasting) and sequentially at 15, 30, 45, 60, and 90 min after the beginning of the CCK-8 infusion. Sequence of the study days was randomized.

Determinations of gallbladder volumes were made by abdominal ultrasonography. The dimensions of the gallbladder, ie, length, height, and width were obtained using sector real-time ultrasound (Phillips 3000; Santa Noa, California) with a 3.0-mHz probe. The gallbladder was scanned subcostally and/or intercostally while patients were in the supine position, and the probe was manipulated so that it followed the appropriate axis and the largest gallbladder dimensions from baseline to 90 min were recorded. No gallstones, wall thickening, or other pathology were identified. Gallbladder volume was calculated by the ellipsoid method according to the following formula: $V = \text{II}/6\ (L \times W \times H)$ where L is the length, W is the width or diameter of the gallbladder, H is the height or depth of the gallbladder as described by Dodd et al (23). Gallbladder contraction was expressed as the max-

TABLE 1. CLINICAL AND LABORATORY DATA OF DIABETIC PATIENTS AND CONTROL SUBJECTS

	Age (yr)	*Weight (kg)*	*Type of diabetes*	*Duration of diabetes (yr)*	*Therapy*	*FVPGC* (mg/dl)*	*Plasma cholesterol (mg/dl)*	*Triglycerides (mg/dl)*	*HgbA1 (%)*
Diabetics									
	30	65.7	IDDM	4	insulin	70	160	70	
	47	66.1	IDDM	41	insulin	140	281	121	9.6
	46	65.5	IDDM	29	insulin	457	267	117	9.4
	37	78.1	NIDDM	1	tolinase	299	254	162	10.2
	52	66.2	NIDDM	5	insulin	154	212	168	39
	39	63.7	NIDDM	18	diet	192	271	192	11.9
	40	88.5	IDDM	5	insulin	313	241	122	12.4
	48	79.9	IDDM	4	diet	106	178	62	7.2
	45	125.7	NIDDM	6	insulin	398	288	374	
	54	77	NIDDM	9	tolinase	198	243	100	
X	44	80.2		10.6		222.8	253.5	148.8	9.8
SD	7.2	20.4		20.4		109.9	47.4	89.2	1.8
Controls									
	24	73.4				81	189	60	
	27	65.3				91	137	67	6.6
	49	54.5				87	171	57	
	50	59.4				73	220	240	6.9
	33	61.7				86	192	95	
X	37.6	62.8				83.4	192.2	99.8	6.75
SD	12.5	7.0				6.3	17.7	78.7	
P value†	0.9	0.02				0.003	0.003	0.3	

*FVPGC = fasting venous plasma glucose concentration.
†*P* values indicate the difference between diabetic and control objects.

imal volume reduction in fasting-initial volume being considered as 100%.

Cholecystokinin Bioassay. Plasma cholecystokinin was measured by bioassay (24). Briefly, cholecystokinin was extracted from plasma by adsorption onto Sep-Pak cartridges previously washed with 5 ml of methanol and 20 ml of water. The cartridges were then washed again with 20 ml of water and the cholecystokinin was eluted with 1 ml of 80% ethanol and 0.2% trifluoroacetic acid. The eluants were collected in 30-ml flat-bottomed incubation vials and dried under a nitrogen stream at 45°C. These vials were subsequently used for incubation with 0.5 ml of rat pancreatic acini suspended in Tris–Ringer buffer. Cholecystokinin was concentrated up to fourfold by adsorbing up to 2 ml of plasma through a single cartridge and eluting the cholecystokinin into a single vial. Pancreatic acini were prepared from 180- to 200-g male Sprague-Dawley rats by collagenase digestion of pancreas in Krebs Henselein bicarbonate buffer as previously described (25). Acini were then incubated with plasma extraction or standard CCK-8 concentrations for 30 min at 37°C. Amylase released into the medium was assayed using porcion yellow coupled starch as substrate. Amylase release expressed as percent of total amylase content was compared with a dose–response curve for CCK-8 in order to calculate the cholecystokinin content of plasma and expressed as CCK-8 equivalents. In this preparation of isolated pancreatic acini, CCK-8 is the most potent stimulus for amylase release. Standard dose–response curves were generated with 1–100 ng/ml sulfated CCK-8. In the bioassay system employed, a detectable effect of CCK-8 was seen at 1 ng/ml and maximal effects were seen at 100 ng/ml. Assay sensitivity was defined as the amount of CCK-8 that produced a statistically different response in amylase release (a response that differed by 2 SD) from that observed with no hormone.

Statistical Analysis. The mean ± SD was calculated for all the results. Differences in response to the meal and hormone stimulation among groups were compared with use of the two-way analysis of variance with repeated measures with the significance at the 5% level. These calculation were done with the assistance of the CLINFO Computer System and BMDP program (26).

RESULTS

The mean age of the diabetic patients (44 ± 7.2 years) was similar to that of controls (37.6 ± 12.5 years, P = NS). The weight of the diabetic patients was significantly higher (Table 1). The median duration of diabetes was 11 years (range 1–41 years). Fasting serum glucose in the diabetic patients, 223 ± 110 mg/dl, was significantly higher when compared to that of controls, 83.4 ± 6.3 mg/dl ($P <$ 0.003). Mean glycosylated hemoglobin (HbA1) in diabetics was 9.8 ± 2% (normal values 4–7%). Blood cholesterol levels in diabetics also were higher than in controls, although triglycerides were not significantly different (Table 1). The questionnaire assessment for subjective symptoms of neuropathy in the diabetics indicated that five diabetics had symptoms. The vibratory testing method for

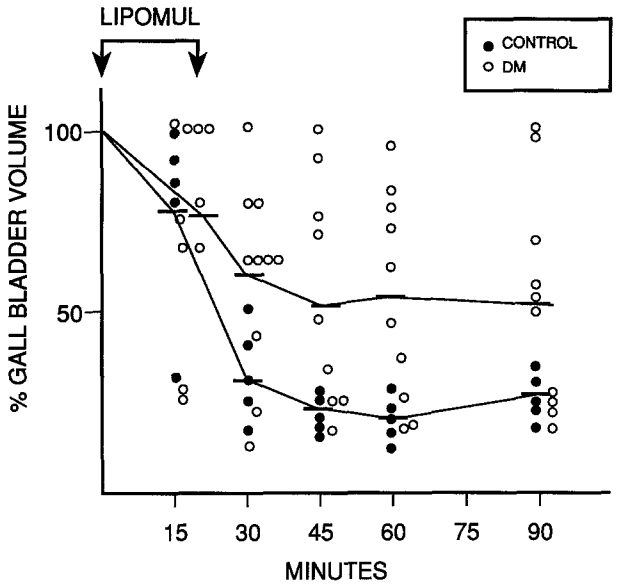

Fig 1. Effect of intraduodenal lipomul infusion on the gallbladder volume in control subjects and diabetic patients. Horizontal bars represent means for each group. There were no significant differences between mean values.

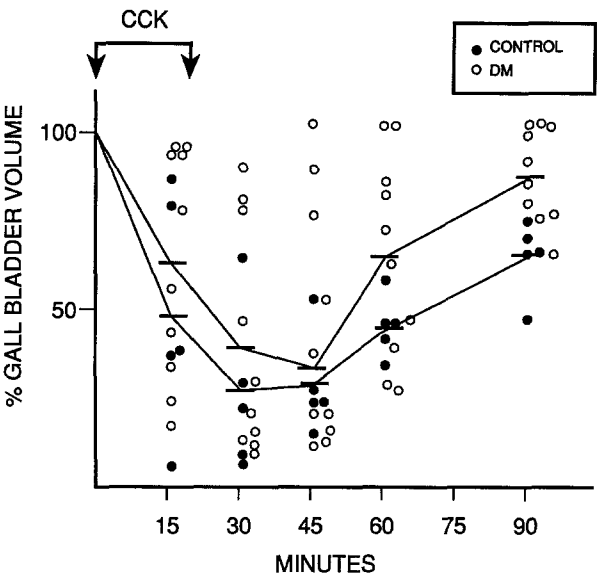

Fig 2. Effect of intravenous CCK on the gallbladder volume in control subjects and diabetic patients. Horizontal bars represent the mean for each group. There were no significant difference between mean values.

peripheral neuropathy demonstrated significant impairment in the lower extremities in diabetics (8.69 ± 3.2 Volts) when compared with that of controls (2.05 ± 0.57 Volts, $P < 0.05$). However, the vibratory tests of the upper extremities in diabetics were not significantly different from those of controls. The thermal testing in diabetics in the upper extremities was 1.22 ± 0.27°C and in lower extremities, 5.13 ± 2.85°C, and were not significantly different from those on controls (1.0 ± 0.57°C upper extremities and 0.82 ± 0.20°C lower extremities). Measurement of the R-R variation ratio to assess autonomic neuropathy (21) revealed that diabetic patients had ratios of 1.16 ± 0.16, similar to that of control subjects (1.27 ± 0.04, P = NS).

Gallbladder Contraction. Control subjects had similar maximal gallbladder contraction with volumes reduced to 21 ± 9% and 24 ± 6% following intraduodenal infusion of lipomul and intravenous CCK-8 administration, respectively (Figures 1 and 2). In contrast, diabetics demonstrated less gallbladder contractility with maximal volume reduction following lipomul and CCK-8 to 49 ± 8% and 47 ± 9%, respectively, although these values did not reach statistical significance ($P > 0.05$) possibly because of dispersion of data (Figures 1 and 2). There was no correlation between the blood glucose concentration, body weight, or percentage of glycosylated hemoglobin and gallbladder emptying. Further analysis of the gallbladder emptying in diabetics revealed two patterns of response to the lipomul infusion: one subgroup of patients ($N = 5$) had gallbladder contraction similar to that of controls with a residual volume less that 40%; we called these patients responders. The remaining five diabetics showed a residual volume of 70% or more and were called nonresponders (Figure 3). Following CCK-8 infusion, two of these nonresponders demonstrated almost complete emptying of their gallbladders with residual volumes of 11% and 15%, while the remaining three had residual gallbladder volumes of 74%, 74%, and 77%, respectively. One of the five diabetic nonresponders and four of the five of the diabetics responders had a R-R interval on the ECG <1.10, probably indicative of autonomic neuropathy (21). No correlation was observed between the presence of autonomic neuropathy, the type of diabetes (insulin-dependent or -independent), and the impairment in gallbladder contractility.

Plasma CCK. Basal plasma CCK was similar in both groups on the two experimental days: diabetics, 2.8 ± 1.4 pM on day 1, 2.1 ± 1.4 pM on day 2; controls, 2.0 ± 1.9 pM on day 1 and 2.0 ± 2.3 pM on day 2). The mean increment of blood CCK concentration following infusion of lipomul in the diabetics (10.9 ± 5.2 pM) was not statistically different from that of controls (11.3 ± 2.5 pM, $P > 0.5$). The blood

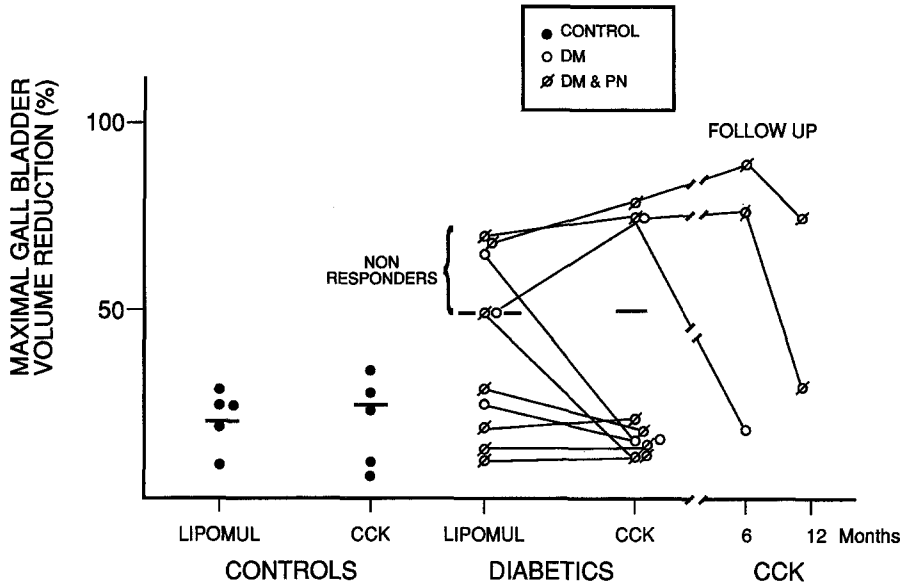

Fig 3. Maximal percent reduction in gallbladder volume in controls and diabetics following intraduodenal lipomul and intravenous CCK. Horizontal bars represent the mean for each group. Follow-up studies with CCK infusions in the three diabetic nonresponders are represented on the right side.

CCK increments during CCK-8 infusion (day 2) also were similar in the diabetics (10.6 ± 5.4 pM) as compared to that of controls (8.4 ± 8.1 pM, P = 0.1). Furthermore, no significant differences were observed in blood CCK increments of diabetic responders (11.1 ± 3.5 pM) when compared to those of nonresponders (13.0 ± 5.2 pM, $P > 0.5$).

Follow-Up Studies. To characterize better the mechanism of failure of the gallbladder to empty in nonresponder diabetics and to determine whether this could lead to an increased incidence of gallstones, three diabetic nonresponders were reexamined 6 and 12 months later. At each visit, ultrasonography was repeated and no stones were found in any instance. In addition, gallbladder emptying was evaluated by ultrasonography each time following infusion of increasing concentrations of CCK-8 (0.1, 1.0, 10, and 100 ng/kg/hr), each dose given for 20 min except the lowest dose, which was infused for 30 min. Gallbladder volume was measured at the end of the infusion of each dose of CCK-8. Results in diabetics were compared to six controls subjects of similar age and sex (unpublished data from our laboratory). Mean (±SD) gallbladder volume in controls was 40 ± 3% and 10 ± 9% following infusions of 10 and 100 ng/kg/hr CCK-8, respectively. One of the diabetics had gallbladder emptying similar to that of controls, with volume reduction to 17% of the initial volume at the six-month follow-up while the other two, remained less responsive with maximal reductions to 75% and 88% of their initial gallbladder volume (Figure 3).

On a further follow-up study on the nonresponders at 12 months, one patient who had a very modest reduction of the gallbladder volume at six months became responsive with a maximal volume reduction to 29% during the highest dose of CCK-8 infusion. The remaining patient remained a poor responder to CCK-8 with a maximal volume reduction to 74% of initial volume.

DISCUSSION

Our current study demonstrates that in this small group of diabetic patients about half of them had normal gallbladder emptying to a fatty meal while the remaining half had impaired gallbladder contraction. Among this last group of nonresponders, normal gallbladder contraction was observed following infusion of CCK-8 in two of them while the remaining three remained nonresponsive. The three nonresponder diabetics were followed up, and we observed that gallstones did not develop in any of them and that two of them later became responsive to graded doses of CCK-8. Given the small size of the diabetic population studied, we cannot extrapolate our findings to larger numbers of diabetics, and it remains to be determined whether unrespon-

siveness of the gallbladder to a meal is a relatively common finding in diabetics. Of interest, however, is that these nonresponsive diabetics did not develop gallstones, at least for the duration of our 12-month follow-up, suggesting that gallstone formation in these patients either may not solely result from impaired gallbladder emptying or that stone formation may result following longer periods of poor gallbladder contractility. Differences in gallbladder emptying in some diabetics do not appear to be due to impaired CCK release since postprandial blood levels of cholecystokinin in diabetics, as determined by a reliable bioassay, do not differ from those of control subjects. Furthermore, no differences in blood CCK increments were observed between responders and nonresponders.

Postprandial gallbladder emptying is mediated by increased circulating levels of cholecystokinin and neurogenic cholinergic impulses (12). Since postprandial plasma cholecystokinin increments in diabetics were comparable to controls, it is possible that the failure of the gallbladder to respond to a meal may be due to impaired cholinergic innervation. This mechanism has been postulated to occur following truncal vagotomy and in most studies on diabetics with visceral neuropathy (28, 30). Visceral neuropathy occurs frequently in long-term diabetics who have peripheral neuropathy (9). The observation that two of the diabetic nonresponders had gallbladder emptying comparable to that of controls during exogenous cholecystokinin is compatible with the hypothesis that this abnormality is due to visceral neuropathy. An unexpected finding was that three diabetics failed to respond to CCK-8 and that this abnormality was reversible in two of them studied at 6 and 12 months of follow-up. This observation is unlikely due to visceral neuropathy since this condition is usually irreversible. In addition, in our study we did not find a correlation between the presence of peripheral neuropathy and/or symptoms suggestive of visceral neuropathy in other segments of the gastrointestinal tract, ie, gastroparesis, severe constipation or diarrhea, and impaired gallbladder emptying. This may suggest that the methodology used to detect neuropathy needs to be more precise. Another possibility is that there may be a discrepancy in some cases between peripheral and visceral neuropathy. It is also possible that other mechanisms, independent of visceral neuropathy, may affect gallbladder emptying. For instance, gallbladder emptying is also determined by the presence of cholecystokinin receptors in the gallbladder and the responsiveness of the smooth muscle fibers in the gallbladder wall (17). The present study did not analyze these parameters. Of interest, however, in an experimental model, hypercholesterolemic prairie dogs have impaired gallbladder emptying and this defect is related to lack of response of CCK receptors in isolated strips of gallbladder smooth muscle (31–33). The intrinsic mechanism of this defect remains to be determined (32). It is not known whether a similar abnormality could occur in diabetic patients. Hypercholesterolemia is often known to occur in diabetics and could be involved in this abnormality. However, when blood cholesterol levels in our diabetics (responders and nonresponders) were analyzed, there were no significantly higher levels observed among those with nonresponding gallbladders.

Based on the normal postprandial cholecystokinin release, it can be ruled out that impaired release of cholecystokinin is the mechanism responsible for impaired gallbladder contraction in this group of patients. Whether reversible gastrointestinal autonomic neuropathy, abnormalities in gallbladder CCK receptors, or abnormalities in the gallbladder smooth muscle contractility are responsible for this gallbladder dysfunction in diabetics needs further investigation.

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