Real-time sonography for screening of gallbladder motility in diabetic patients:
Relation to autonomic and peripheral neuropathy

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ORIGINAL ARTICLE

Abstract

OBJECTIVES: Diabetes mellitus is known as one of the factors causing the cholesterol gallstone. Gallstone incidence is about 30% in diabetic patients over 20 years of age. Pathophysiology is still not clear. The aim of the present study was to investigate gallbladder (GB) functions in diabetic patients and determine its relationship with peripheral and autonomic neuropathy.

DESIGN: Study was performed between October 2001 and may 2002 in fifty-one diabetic patients of similar age and weight. Diabetic patients (n=51) were chosen randomly among diabetic patients, who were being followed in Diabetes Out-patient clinics of Selcuk University, Meram Medical Faculty. Twenty-eight control subjects were chosen from healthy volunteers. We measured fasting and post-prandial gallbladder volumes and ejection fractions by real-time ultrasonography. The patients were divided into three groups; group A (n=18) had no diabetic autonomic and peripheral neuropathy, group B (n=13) had diabetic peripheral neuropathy, group C (n=13) had diabetic autonomic neuropathy.

RESULTS: No significant difference in any biochemical parameters between diabetic and control group could be found. Fasting gallbladder volume was significantly higher in the diabetic group (5.31 ± 0.28 cm^3) compared to control group (4.19 ± 0.25 cm^3, p<0.01). But there was no difference within diabetic subgroups. Gallbladder ejection fraction was significantly reduced in diabetic patients in groups B and C ($29.7 \pm 1.43\%$, $28.7 \pm 1.28\%$) compared to group A ($44.8 \pm 2.4\%$; p<0.05, p<0.025 respectively).

CONCLUSIONS: Cholesterol crystal formation as a result of increased gallbladder volume and decreased ejection fraction in diabetic patients may result from hypotonicity and stasis and thus this may lead to gallstones.

Introduction

Hypertriglyceridemia and obesity together with impaired gallbladder motility in diabetics are risk factors for gallstone formation [1,2,3]. Neurologic control of gallbladder emptying is under parasympathetic and sympathetic nervous systems where parasympathetic system controls contractility, sympathetic system controls relaxation. Hepatobiliary infections may help in stone formation [4]. The reduced motility of gallbladder can be caused by autonomic nervous system dysfunction and defective response to gastrointestinal hormones such as cholecystokinin, motilin and secretin [5]. There are limited data concerning peripheral neuropathy and gallstone relation.

In the present study, we aimed to investigate gallbladder functions in diabetic patients and determine its relationship with peripheral and autonomic neuropathy.

Materials and methods

Study was performed between October 2001 and May 2002 in age, sex and weight matched fifty-one diabetic patients and twenty-eight control subjects. Diabetic patients were chosen randomly among diabetic patients, who were being followed in Diabetes Outpatient clinics of Selcuk University, Meram Medical Faculty. Control subjects were chosen among healthy volunteers. Patient group consisted of 23 male and 28 female patients (mean age 52.21±12.04). Control group consisted of 15 male, 13 female subjects (mean age 52.55 ± 9.64). Inclusion criteria for control subjects were absence of gastrointestinal disorders and cholelithiasis and diabetes mellitus.

Patients with severe anemia (Hb< 10 gm), renal disease (serum creatinin > 1.5 mg/dl), endocrine disease (thyroid, adrenal or parathyroid abnormalities), heart disease (congestive heart failure or history of arrhytmias), and previous history of gastrointestinal disorders such as severe constipation, persistent diarrhea, gallbladder disease, cholecystectomy or gallstones as determined by screening ultrasonography were excluded from the study

In all patients, sex, age, body mass index (BMI), presence and duration of diabetes, total cholesterol, triglycerides, HDL, LDL, ALT, AST, total bilirubin, hemoglobin A1c and fasting blood glucose were considered. The following patients were considered diabetic, using recommendations of Expert Committee with FPG of 126 mg /dl and/or a 2-h post oral glucose tolerance test (OGTT) plasma glucose level of 200 mg/dl on more than one occasion [6].

Blood glucose, serum triglycerides, cholesterol, HDL, LDL, AST, ALT, total bilirubin levels were evaluated by routine laboratory methods.

Evidence for peripheral neuropathy was revealed by measurements of nerve conduction velocities. Subjects were questioned specifically about subjective symptoms of peripheral neuropathy (paresthesia, numbness, hyperesthesia, spontaneous burning pain), and examination for abnormalities of light touch using cotton wool, joint position sense, superficial pain using a sharp pin, and ankle and knee reflexes. Motor nerve conduction studies were performed on the left leg and arm using a Nihon Kohden Neuropack 2(MEB-7102) K EMG. Peroneal and median nerve motor conduction velocity <41 mls, ulnar nerve sensory conduction velocity <40 mls, peroneal nerve conduction < 50 mls, sural nerve sensory conduction velocity < 40 mls were considered pathologic. Subjects were defined as having a clinical peripheral neuropathy if they had symptoms and/or signs plus one or more abnormal neurophysiologic variables [7].

Autonomic neuropathy was defined by having at least two abnormal cardiovascular reflexes, including: 1) an impaired heart-rate response to the valsalva maneuver, standing, and deep respiration, 2) postural fall in systolic blood pressure of at least 30 mmHg [8]. The diabetic patients were classified into three groups: Group A: 18 patients without clinical evidence of peripheral and autonomic neuropathy. Group B:13 patients had diabetic peripheral neuropathy but no evidence of autonomic neuropathy. group C:13 patients with advanced autonomic neuropathy but no evidence of peripheral neuropathy.

The gallbladder areas were measured by a real-time ultrasound and computer unit (Aloka UST-979, 3.5 mHz electronic convex probe, Japan). The probe was placed on the right subcostal area while patients were in the supine position and angled to obtain images showing the largest longitudinal diameter of the gallbladder. Gallbladder volume was calculated by the ellipsoid method according to the following formula:

V=0.52 (LxWxH) where L is the length, W is the width or diameter of the gallbladder, H is the height or depth the gallbladder. Gallbladder images were obtained after a standard breakfast consisted of an egg, milk and pastry (containing 695 kcal, 19.2 gr carbohydrate, and 9 gr fat).The percentage of emptying (ejection fraction, EF) was calculated using the following formula [9,10]:

$$EF\ (\%): (\text{fasting GB volume-postprandial GB volume / fasting GB volume}) \times 100$$

Statistical analysis: the mean ± SD was calculated for all the results. Comparison between continuous variables such as age, BMI, known duration of diabetes, biochemical data, ejection fraction was performed by ANOVA or student's *t-test* for unpaired values. Values with p < 0.05 were considered significant.

Results

There was no significant difference in terms of biochemical indices between controls and any group of diabetics. In particular, those subgroups showing autonomic and peripheral neuropathy were found to have been suffering from diabetes longer than their counterparts. However, the difference was not statistically significant (9.0 ± 6.2, 11.6 ± 8.7 vs 7.5 ± 5.2 years). HbA1c were 7.7 ± 2.1%, 8.16 ± 1.6%, and 8.14 ± 1.69%

in groups A, B, and C respectively; not significantly different from each other (Table 1).

The average volume of the gallbladder in diabetics was 5.31 ± 0.28 cm^3 during fasting and 3.33 ± 0.19 cm^3 postprandial, which seemed to be significantly higher than the average volume of the control group (4.19 ± 0.25 cm^3 fasting and 1.69 ± 0.14 cm^3 after feeding) ($p < 0.01$). Fasting gallbladder volume was not significantly different between any of the subgroups of diabetics (A:5.02 ± 0.34, B:5.23 ± 0.37; C:5.52 ± 0.46 cm^3) (figure 1).

The average ejection fraction value of gallbladder in diabetic group was 36.86 ± 1.31, whereas that of the control group was 60.14 ± 2; statistical difference being significant ($p < 0.001$). In the diabetic patients gallbladder ejection fraction, 45 minutes after a meal, was $44.8 \pm 2.4\%$, $29.7 \pm 1.43\%$, $26.7 \pm 1.28\%$ in groups A, B and C respectively. There was no significant difference between group B and C, however, in groups B and C, maximum contraction was significantly reduced compared to group A ($p < 0.05$, $p < 0.025$ respectively) (Figure 2).

Discussion

The frequency and nature of gallbladder disorders in diabetes mellitus is still controversial [1]. In a Danish cross-sectional study, Jorgensen [11] found no association between diabetes mellitus and gallstones. However Chapman et al [12] revealed that subjects of both sexes with type 2 diabetes mellitus, had higher prevalence of gallstones than controls. In a case-control study, Hayes et al found no association between diabetes and cholelithiasis in diabetic patients and controls [13]. Nonetheless, various observations support the association of cholelithiasis with diabetes in diabetic subjects, the biliary saturation index is increased and gallbladder motility is decreased [14,15]

In the present study, we demonstrated that the fasting gallbladder area measured by ultrasound was higher in diabetic patients than normal subjects, and gallbladder contraction was impaired in patients with diabetics compared with controls.

The results of studies of gallbladder function in diabetic patients have not been consistent [16]. The mech-
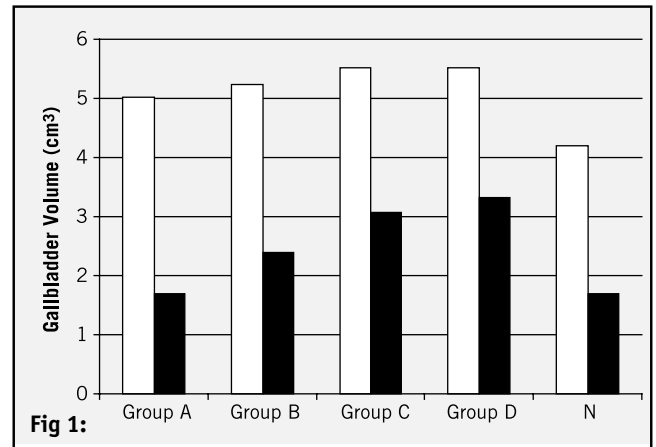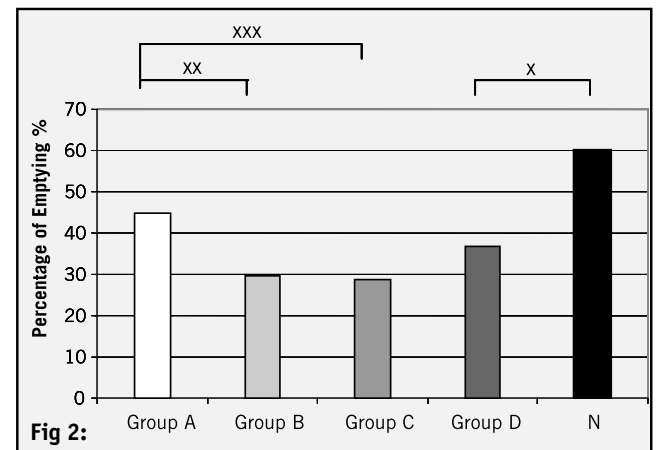

Fig 1:

Fig 2:

A: Group A diabetics (18)
B: Group B diabetics (13)
C: Group C diabetics (13)
D: All diabetic patients (51)
N: Control (28)

Fig 1: Fasting and postprandial gallbladder volumes in diabetic patients and controls. Fasting gallbladder volume was not statistically significant, between any of the groups of diabetics; but the average volume of the gallbladder of all diabetic patients was significantly higher than the average volume of the control groups ($p < 0.01$). Clear bar: fasting gallbladder volume. Black bar: post prandial gallbladder volume.

Fig 2: Ejection fraction, 45 minute after a meal in controls, groups A, B, C and D. $^x p < 0,001$, $^{xx} p < 0,05$ $^{xxx} p < 0,025$

Table 1: Charactheristics of controls and diabetics

	Autonomic neuropathy	Peripheral neuropathy	Without peripheral and autonomic neuropathy	control
Age (yr)	51.6 ± 9.2	56.2 ± 8.8	48.75 ± 11.6	52.55 ± 9.6
BMI (kg/m2)	29 ± 5.20	30.7 ± 6.06	30.4 ± 5.80	28.4 ± 5.42
Duration (yr)	11.6 ± 8.7	9.0 ± 6.2	7.5 ± 5.2	
Cholesterol (mg/dl)	207.1 ± 41.1	204.3 ± 29.7	198.6 ± 30.7	201 ± 30.4
Trigliyserid (mg/dl)	178.4 ± 97	196.6 ± 80.4	184 ± 68.6	158 ± 17.5
LDL	149.8 ± 82.1	152 ± 90.8	147.6 ± 84.8	152.4 ± 68.6
HDL (mg/dl)	41.3 ± 9.5	40.4 ± 10.2	39.7 ± 8.6	44.6 ± 10.8
HbA1c (%)	8.14 ± 1.69	8.13 ± 1.52	7.9 ± 1.82	
T. bilirubin	0.8 ± 0.21	0.82 ± 0.26	0.86 ± 0.22	0.78 ± 0.34
AST	20.4 ± 2.8	21.6 ± 4.4	22.8 ± 6.2	19.4 ± 5.7
ALT	23.7 ± 3.4	26.8 ± 5.4	25.7 ± 4.8	21.5 ± 3.4

anism of gallbladder hypomotility in gallstone disease remains unknown. The combined effects of poor emptying and possibly decreased ejection fraction rate and increased fasting volume could lead to bile stasis within the gallbladder and the formation of stones. The vagus nerve stimulation and cholecystokinin (CCK) in plasma are the main factors causing the contraction of the gallbladder [17,18]. On the other hand, it is reported that the diabetic patients with autonomic neuropathy respond little to the cholecystokinin [15, 19], however they have higher postprandial blood cholecystokinin levels then those without autonomic neuropathy [4]. Furthermore, Shaw et al reported this was not due to impaired cholecystokinin release [14]. Stone et al documented that in diabetic patients with autonomic neuropathy, gallbladder contraction in response to CCK infusion was reduced. Another possibility is that the smooth musculature of gallbladder of diabetic subjects is less responsive to the CCK stimulus [19]. Gallbladder dysfunction in diabetics, could be secondary to inappropriate CCK secretion. It is also known that the contraction of gallbladder is caused by the stimulation of the vagus nerve [20]. One hypothesis is that a functioning gallbladder requires an adequate vagal tone although the role of the vagus in gallbladder emptying is still controversial [21]. It is possible that the failure of the gallbladder to respond to a meal may be due to impaired cholinergic innervation. In our study, in particular, the autonomic and peripheral neuropathic subgroups showed a significant reduction of ejection fraction value compared with their counterpart subgroup without autonomic and peripheral neuropathy. It was shown that volume of gallbladder increase during fasting and EF is reduced after a test meal in autonomic neuropathic subgroups [3,15,19,22] whereas an author found no significant difference [23]. We suggest that impaired contractility of the gallbladder in diabetic patients with autonomic and peripheral neuropathy may predispose to the subsequent development gallstones.

We found that diabetes history was longer in patients with peripheral and autonomic neuropathy then those without these complications, as such was reported in other studies [14]. Mitsukawa et al showed in a group of diabetic patients with autonomic neuropathy, gallbladder rate in response to egg yolk slightly, but significantly impaired compared to normal subjects [4]. There appears to be a correlation between the presence of diabetic cholecystoparesis and peripheral neuropathy. However, Shaw et al did not find a correlation between the presence of peripheral neuropathy, autonomic neuropathy and the impairment of gallbladder contractility [14]. In our study, we demonstrated that gallbladder EF was impaired in diabetic patients with peripheral neuropathy groups similar to the study of Chaudri [24].

As a conclusion, we suggest that, autonomic and peripheral neuropathy are important causes of impaired gallbladder contraction in diabetes mellitus. Those patients with autonomic and peripheral neuropathies must be observed for gallstones. Additionally, histochemical studies in gallbladder wall may also help clarify the pathophysiology of gallbladder stasis.

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