

Research Article

Gall bladder dysfunction in chronic diabetics (type 2): an ultrasonography based prospective study

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ABSTRACT

Background: Type 2 diabetes mellitus is commonest endocrine disorder now a days and its prevalence is continuously rising in India due to spread of modern life style so its associated complications are also increasing. Gall bladder is one of the commonly affected organs in chronic diabetics, most probably due to autonomic neuropathy which adversely affects gall bladder motility and provokes bile stasis.

Methods: This institution based prospective study had been performed among 100 chronic diabetics; randomly selected from diabetic clinic of department of medicine, people's college of medical science and research centre, Bhopal M.P. India. Only those patients selected for study who have type 2 diabetes mellitus more than 5 yr and have well controlled sugar levels. 100 controls/volunteers were selected for comparative evaluation. All patients and volunteers had undergone abdominal ultrasonography for any existing hepatobiliary pathology and to measure fasting and post fatty meal gall bladder volume.

Results: Among 100 chronic diabetics seventy-six (76%) patients didn't show any hepatobiliary abnormality however cholelithiasis was seen in thirteen (13%) patients, cholecystitis in five (5%) patients and sludge was seen in six (6%) patients. In group of 100 controls ninety-one (91%) didn't show any hepatobiliary pathology however cholelithiasis was detected incidentally in four (4%) persons, cholecystitis in two (2%) persons and sludge in three (3%) persons. Significant difference is observed in fasting gall bladder volume of chronic diabetics and controls (p value- 0.001). Major difference is also observed in percentage of gall bladder contraction among chronic diabetics and controls (p value- 0.001).

Conclusions: Higher fasting gall bladder volume and decreased percentage of contraction both are observed in patients of chronic diabetes mellitus attributed to autonomic neuropathy. Prolonged stasis of bile leads to complications e.g. cholelithiasis, cholecystitis and sludge deposition as late outcome. Hepatobiliary ultrasonography in chronic diabetics can be used as screening tool for early diagnosis of complication and to avoid its serious consequences when presents in emergency and undergone for surgery.

Keywords: Chronic diabetics, Fasting gall bladder volume, Percentage of contraction, Ultrasonography, Cholelithiasis, Cholecystitis, Autonomic neuropathy

INTRODUCTION

Since long time diabetes mellitus is one of the most common endocrine disorder and now a day it is on the rise due to advancing modern life style; characterised by

multiple metabolic abnormalities which leads to long-term multi organ complications involving hepatobiliary system, kidneys, gastrointestinal tract, nerves, and blood vessels, thereby causing serious morbidity and mortality. Few previous studies had pointed towards an increased

prevalence of gall bladder dysfunctions and its complications in diabetics.¹⁻³ Those have been attributed to cholecystomegaly and impaired motility of gall bladder, mainly due to autonomic neuropathy commonly seen in chronic diabetics. Though prolonged bile stasis is the most important factor for gallstone formation but other risk factors i.e. age, sex, obesity, genetic predisposition, drugs, parity, diet, hyperlipidaemia, and ileal resection also contribute in it.⁴ This study was undertaken to compare gall bladder volumes in chronic diabetics and controls. Ultrasonography is preferred modality of choice to assess gall bladder volume because it is safe, non-invasive, less expensive, less time consuming, and accurate. This study was also intended to correlate gall bladder volume in patients of chronic diabetes with other parameters of patient like age, sex, body mass index (BMI), parity and hyperlipidaemia.

In addition to different manifestations in many other systems of body, autonomic neuropathy is responsible to various manifestations in the gastrointestinal tract such as nocturnal diarrhoea, oesophageal dysmotility, gastropathies, constipation and gallbladder dysfunction which is consequence of vagal neuropathy and leads to decreased gastrointestinal motility. The duration of diabetes mellitus has significant positive correlation with prevalence of gallbladder disease. Type of therapy for treatment has no significant association and the fasting plasma glucose level is inversely associated with gall bladder disease.⁵

Involvement of gall bladder in diabetic autonomic neuropathy is usually manifested in the form of higher incidence of gall stones and a significant increase in gall bladder volume⁶ with poor concentration and poor visualization, with lack of symptoms of gallbladder disease.⁷ The present study has aim to find out the prevalence of gallbladder diseases in patients of type 2 chronic diabetes, correlation in duration of diabetes with gall bladder disease and comparison of gallbladder dysfunction in patients with and without autonomic neuropathy as well as normal individuals.

Reduced gall bladder motility in chronic diabetics due to autonomic neuropathy together with hypertriglyceridemia and obesity is a major risk factor for cholelithiasis.⁸⁻¹⁰ Gall bladder emptying is controlled by both, sympathetic and parasympathetic nervous system where parasympathetic system controls contractility and sympathetic system controls relaxation. Reduced motility of gall bladder is attributed to dysfunction of autonomic nervous system dysfunction and defective response to gastrointestinal hormones e.g. cholecystokinin, motilin and secretin.¹¹

Aims and objectives

The aims and objectives of the study were,

1. Study the prevalence of gallbladder dysfunction in chronic type 2 diabetes mellitus.
2. Determine correlation of gall bladder disease with duration of diabetes mellitus.
3. To compare prevalence of gall bladder diseases in patients of chronic diabetes mellitus and non-diabetic controls/volunteers.

METHODS

The present descriptive cross sectional study was conducted on 100 diabetic patients enrolled from the diabetes clinic of the Department of Medicine, Peoples College of medical science and research centre, Bhopal, MP, India. The diagnosis of diabetes in these patients was in accordance with WHO criteria i.e., fasting plasma glucose level ≥ 126 mg/dl, and ≥ 200 mg/dl plasma glucose level after 2 hr of ingestion of standardised 75 gm glucose. An informed consent was taken from all the subjects in the study and control groups. Study design and its protocol was approved by the institutional ethical committee.

Selection of study group

Total 100 patients were randomly selected for the study among patients regularly attending diabetic clinic of this hospital and following our criteria's of selection.

Inclusion criterion

1. Patients of type 2 diabetes mellitus diagnosed since 5 yr or more.
2. Functioning gall bladder with well controlled blood sugar levels.
3. Patients of 30 to 60 yr age group.

Exclusion criterion

1. Patients with history of pre-existing hepatobiliary or gastrointestinal disease.
2. Those diabetic patients who are taking antihypertensive drugs also, which can interfere with autonomic functions.
3. Obese patient with history of major cardiac arrhythmia.
4. Pregnant females.
5. Patient with history of cerebrovascular accident.

Selection of control group

100 healthy volunteers have been selected in this group. Only those have been selected who don't have morbid obesity, pregnancy or gastrointestinal, renal, and cardiac diseases.

Statistical analysis

Statistical analysis done by using statistical Package of Social Science (SPSS Version 19; Chicago Inc., USA).

Data comparison performed by applying specific statistical tests i.e. Chi Square test, Student t test were applied to find out the statistical significance of the comparisons. Qualitative variables were compared using proportions and quantitative variables were compared using mean values. Significance level was fixed at $P \leq 0.05$.

Method to measure gallbladder volume

Gallbladder volume was measured in all the subjects after 12 hours overnight fasting by using a 3.5 to 5 MHz convex transducer in Wipro GE Voluson S6 and medison accuvix ultrasound and colour Doppler machine. The greatest length (L), maximum transverse width (W), and highest anteroposterior dimensions (H) were measured and documented. All the measurements were recorded by first author of the study on two consecutive days, and the average of the two measurements was considered as the final fasting gall bladder volume for the case and control. This protocol was adopted to ensure the reproducibility of the results.

The gall bladder volume was calculated by this formula¹³

$$= \frac{\pi \times L \times W \times H}{6}$$

Where, L = Length, W = Width and H = Height of gall bladder.

Many other related findings e.g. gallbladder wall thickness, presence of stones, sludge or neoplasia were searched and recorded.

Gall bladder motility was observed by measuring fasting and post meal gallbladder volumes. Post meal volume was taken one hour after giving fatty meal i.e. four slice of bread with 30 gm butter. The percentage of gallbladder contraction was calculated by the formula.¹⁴

$$\frac{\text{Fasting Gall bladder volume} - \text{Post fatty meal gall bladder volume}}{\text{Fasting gall bladder volume}} \times 100$$

Table 1: Prevalence of gallbladder disease among study group & control group.

Groups	Gall bladder disease				
	No Gall bladder disease No (%)	Cholelithiasis No (%)	Cholecystitis No (%)	Sludge No (%)	Total No (%)
Chronic Diabetic (n=100)	76 (76.0%)	13 (13%)	5 (5%)	6 (6%)	24 (24%)
Controls (n=100)	91 (91.0%)	4 (4%)	2 (2%)	3 (3%)	9 (9%)
Chi Square Value	8.40				
P Value	0.038(S)				

No (%) - Number (percentage), (S)-Significant

The results of the study have been compiled, tabulated and statistically analyzed for comparisons.

RESULTS

Mean age of diabetic Patient was 52 yr in study group and 50.2 yr in control group.49% of diabetics were males and remaining 51% were females, Figure 1 whereas in control group male to female ratio was equal, means 50 males and 50 females. The mean duration of diabetes in patients was 9.5 years.

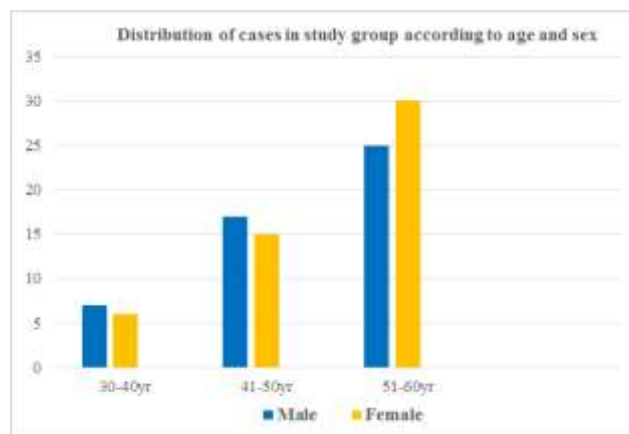


Figure 1: Distribution of diabetic patients (n=100) according to age and sex.

Prevalence of gallbladder disease among both study groups is shown in Table 1, which revealed higher prevalence of gall bladder disease in group of chronic diabetics as compared to group of controls (p value-0.038).

In Table 2 correlation of duration of diabetes mellitus to gall bladder disease has been demonstrated which showed rise in prevalence of gall bladder disease with increasing duration of diabetes mellitus (Figure 2).

Table 2: Association between gall bladder Disease and duration of diabetes mellitus.

Duration of Diabetes	Gall bladder disease			Total No (%)
	Cholelithiasis No (%)	Cholecystitis No (%)	Sludge No (%)	
5-10 year	2	1	1	4
11-15 year	3	1	2	6
≥ 16 years	8	3	3	14
Chi Square Value	0.379			
P Value	0.984(NS)			

No. (%) - Number (percentage), NS-non significant

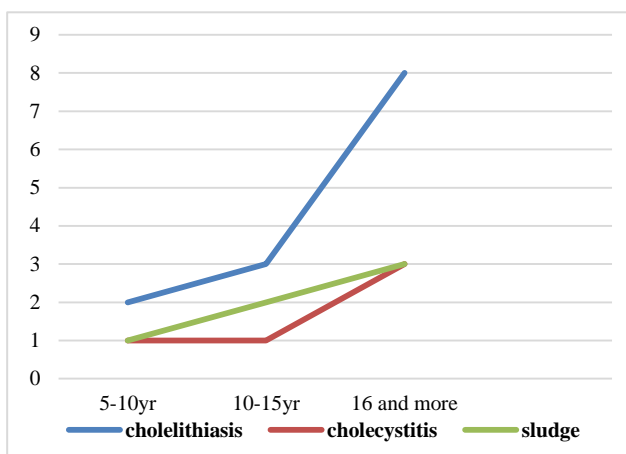


Figure 2: Showing rise in prevalence of gall bladder disease with duration of diabetes.

From Table 3, it was concluded that fasting gall bladder volume in chronic diabetics was higher than that of controls and the difference of values was found to be highly significant (p value 0.001) (Figure 3).

Table 3: Fasting gall bladder volume among study group & control group.

Groups	Mean fasting gall bladder volume in CC		Student 't' Test Value	Significance P – value
	Mean	SD		
Chronic Diabetics (n=100)	45.27	3.87	31.627	0.001(HS)
Controls (n=100)	29.88	2.95		

SD- standard deviation, HS-highly significant, CC -cubic centimeter

From Table 4, it has been cleared that the percentage of contraction of gall bladder had reduced markedly in chronic diabetics as compared to controls (p value-0.001).

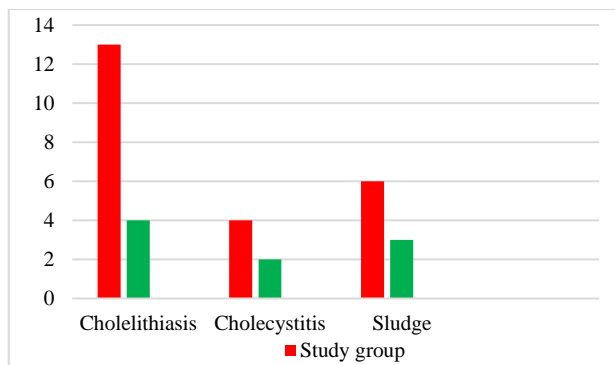


Figure 3: Showing comparison in prevalence of gall bladder disease between study and control group.

Table 4: Percentage of contraction of gall bladder volume among both study groups.

Groups	Mean percentage of gall bladder contraction		Student 't' Test Value	Significance P – value
	Mean	SD		
Chronic Diabetics (n=100)	43.56%	8.87	14.678	0.001(HS)
Controls (n=100)	60.10%	6.95		

SD- standard deviation

Table 5 shows a comparative evaluation of results of the study with previous similar type of studies and no major difference is observed in the results.

Table 5: Comparison in prevalence of gall bladder disease among different studies.

Sr. No.	Previous study	Prevalence of gall bladder disease	
		In diabetics	In controls
1.	Raman, 20025	32.00%	6.70%
2.	Jorgenson, 19898	32.80%	17.30%
3.	Chapman, 19982	21.40%	14.00%
4.	Singh	26.0%	10.0%
5.	Present study	24.0%	9.0%



Figure 4: Fasting gall bladder volume measurement in a control.



Figure 5: Fasting gall bladder volume measurement in a 60 yr old chronic diabetic with cholelithiasis (arrow) and acute cholecystitis.



Figure 6: (a) Ultrasonography image is showing an incidentally detected calculus in gall bladder lumen (arrow) in a chronic diabetic patient. (b) Ultrasonography image is showing sludge in gall bladder lumen (arrow).



Figure 7: (a) Ultrasonography image is showing chronic acalculus cholecystitis in a control (arrow). (b) Ultrasonography image is showing cholelithiasis (arrow) with acute cholecystitis.

DISCUSSION

According to the data of public health foundation of India more than 62 million peoples are suffering from diabetes mellitus at the time and this number is continuously rising so India is on the way to turn Diabetes capital of the world.¹⁵ The diabetes epidemic in the country had killed 10 lakh people in 2011.¹⁵ Contrary to general belief, diabetes mellitus affects more people in rural India (34 million) than affluent urban population (28 million). The gap in the number of diabetic men and women in

India is also declining. In comparison to 33 million males, 29 million women are affected by diabetes mellitus in India. By 2030, India's diabetic population figures expected to cross the 100 million mark. Average age of onset of type 2 diabetes mellitus and peak prevalence age in India is 10 yr less than Japanese and Chinese population.¹⁶ According to the World Health Organisation (WHO) data nearly 200 million people all over the world are suffering from diabetes mellitus and this number is expected to be doubled by the year 2030. Though diabetes mellitus is caused by a complex interaction of genetic and modern lifestyle factors, the most obvious reason for rise in the number of young diabetics is their frenetic lifestyle.¹⁵

There are many similarities between the gastrointestinal symptoms following surgical vagotomy and chronic complications of diabetes mellitus which suggest the involvement of autonomic nervous system in diabetic neuropathy.¹⁷ Various studies^{12,13,18} conducted in the past at different institutions as mentioned in Table no. 5 have shown a positive correlation between chronic diabetes mellitus and gall bladder diseases. The present study also has positive correlation between these two. It has been proved that there is increased prevalence of gall bladder dysfunction among chronic diabetics and chronic diabetics tend to have comparatively larger gall bladder volume with reduced responsiveness to fatty meals which might lead to prolonged stasis of bile and its complications like sludge, cholelithiasis and cholecystitis. Although definite pathophysiology of gall bladder dysfunction in chronic diabetics is still unclear and under research, motor abnormalities of gallbladder is considered as culprit and one of the proposed mechanisms. These motor abnormalities include enlarged gall bladder with impaired contractility due to vagal visceral neuropathy which leads to complications.

Impaired gall bladder emptying was found more among chronic diabetics having autonomic neuropathy. Since gall bladder dysfunctions usually remain clinically silent among diabetics for long time, patients may suddenly present with catastrophic complications like acute cholecystitis and may require emergency cholecystectomy. Because increased mortality and morbidity is associated with emergency cholecystectomy in chronic diabetics, prophylactic cholecystectomy may be advisable in asymptomatic patients when evidence of nonfunctioning/malfunctioning gall bladder is found in ultrasonography³ and this thing proves the importance of this study.

Autonomic neuropathy of the gastrointestinal tract in chronic diabetics manifested in several forms like oesophagopathy, gastroparesis, enteropathy and biliary tract dysfunctions. Frequently quoted reasons for the increased prevalence of cholelithiasis in chronic diabetics include; impaired gall bladder motility, decreased postprandial cholecystokinin (CCK) release, decreased sensitivity of gall bladder smooth muscles to CCK,

decreased number of CCK receptors in the gallbladder wall and supersaturation of bile.¹

Neural control of gallbladder emptying is mediated by both parasympathetic and sympathetic innervation; the former is responsible for gallbladder contractility and the latter mediate in gall bladder smooth muscle relaxation.¹ Postprandial release of CCK causes gallbladder contraction and release of bile in GI (gastrointestinal) tract. Motility disorder in patients of gall stone are manifested by increased fasting gall bladder volume, decreased ejection fraction, decreased ejection rate with increased residual volume of the gall bladder.¹ This study has demonstrated increased fasting gallbladder volumes in type 2 chronic diabetics in comparison to healthy controls. These findings have been authenticated by earlier researcher's also.¹⁹⁻²⁵ They also measured gallbladder emptying rate and extent as a measure of gallbladder motility and found that the gallbladder emptying rate and/or the gallbladder emptying were also reduced significantly in chronic diabetics.¹⁹⁻²⁵

Further it was observed in above studies like our study that increased fasting gallbladder volume and decreased ejection fraction, both were associated with presence of autonomic neuropathy. We have not measured gallbladder emptying rate and extent due to logistical constraints, but if done, would further elucidate the role of autonomic neuropathy in diabetic cholecystopathy. Further indirect association of autonomic neuropathy with cholesterol gallstones is derived from various studies which show an increased prevalence of gallstones in non-diabetic patients having high spinal cord injury, decreased gallbladder emptying in response to cephalic stimulation in diabetic patients with autonomic neuropathy,²⁶ normal postprandial blood CCK levels in diabetics,¹² and a good motility response after infusion of CCK or its analogues in diabetics with autonomic neuropathy.^{26,27}

So we can hypothesize that chronic diabetic autonomic neuropathy is a major cause of cholecystopathy and that hormonal response to fatty meals and sensitivity of gall bladder to hormonal stimulation remains almost unchanged in diabetic patients with or without autonomic neuropathy however, autonomic neuropathy is not entirely responsible for the cholecystoparesis. Braverman DZ found in his study that diabetic cholecystoparesis was not corrected by metoclopramide, a known cholinergic stimulant and antiemetic drug.²⁸ In contrast, Dhiman et al found improved gallbladder emptying in response to cisapride, another cholinergic stimulant.²⁹ Annese et al³⁰ have found in their study that autonomic neuropathy in chronic diabetics have poor predictive value for motor disorders and suggested the coexistence of other pathophysiologic mechanisms e.g. increased bile lithogenicity, delayed gastric emptying,³¹ and reduced alpha-adrenergic tone of gallbladder.³²

Body mass index (BMI) had exhibited significant positive correlation with gall bladder volume in previous study.³³ Jain A et al found obesity in 64% patients in their study. With advancing age, lean body mass decreases and percent adiposity increases, but there may be minor or no change in total body weight. Hence, it is necessary to look for central or truncal obesity and not BMI, which may not depict true obesity. Hypertension is well-recognized as an insulin-resistant state. Hypertension is a frequently associated comorbidity in chronic diabetics and its prevalence and morbidity increases with advancing age.³³ In people with type 2 diabetes mellitus, hypertension is a major risk factor for cardiovascular disease. Elderly patients (>60 yr) with hypertension and diabetes mellitus have higher morbidity and mortality risk. Eighty percent patients had associated hypertension in a study conducted by Jain A et al.³³

Increasing age also has significant positive correlation with gallbladder volume in this study, which can be explained by age, related spontaneous autonomic denervation leading to bile stasis due to hypo motility, increased bile viscosity, and increased cholesterol content in bile. There was no correlation of gender with gallbladder volume in this study as seen in earlier study²⁹ but significant correlation was found with duration of diabetes mellitus. Increased LDL levels exhibit positive correlation with increased gallbladder volume in male type 2 diabetics in our study. Although hypertriglyceridemia is a well-known risk factor for cholelithiasis but the role of hypercholesterolemia in gallbladder hypo motility is uncorroborated. A study conducted by Wilson et al³⁴ and they found that no change was observed in gallbladder emptying; before and after three months of treatment with simvastatin and bezafibrate in female type 2 diabetics also having hyperlipidemia.

Thus, our study recapitulates the fact that cholecystopathy in chronic type 2 diabetics, may predispose these patients to cholelithiasis and it is not uncommon. This fact raised the risk of complications of gallstone disease and its treatment including both surgical and medical. A definite significant association of autonomic neuropathy and cholecystomegaly has been found in our study and it signifies a thorough evaluation for autonomic neuropathy in all chronic diabetics. All chronic diabetics should be evaluated for the presence of impaired pre and post meal gallbladder volumes, postprandial emptying, gallbladder sludge and stones; all markers of progression to undisguised gall stone disease.

CONCLUSIONS

Higher fasting gall bladder volume and decreased percentage of contraction both are observed in patients of chronic diabetes mellitus attributed to autonomic neuropathy. Prolonged stasis of bile leads to complications e.g. cholelithiasis, cholecystitis and sludge deposition as late outcome. Hepatobiliary

ultrasonography in chronic diabetics can be used as screening tool for early diagnosis of complication and to avoid its serious consequences when presents in emergency and undergone for surgery.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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