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RESEARCH ARTICLE

STUDY OF AUTONOMIC DYSFUNCTION AND GALLBLADDER DISEASE IN TYPE-2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Background: Diabetes mellitus is a disease of increasing incidence which leads to various complications over a period of time. Autonomic neuropathy is one such complication which may lead on to gallbladder dysmotility and gallbladder stones.

Objectives: Type II Diabetes Mellitus patients were evaluated for gallbladder disorders, to find out the incidence of autonomic dysfunction in type 2 diabetes mellitus and correlate it with presence of gall bladder disorders.

Material and Methods: The present study was conducted in 50 cases of type 2 diabetes mellitus and 25 healthy age and sex matched normal individuals were taken as controls. The cases as well as the controls underwent ultrasonographic examination for gall bladder volume, wall thickness, intraluminal mass and contraction in response to fatty meal. Data thus collected was compared and analysed statistically by using students 't' test and chi-square test.

Results: Mean postprandial gallbladder volume was 20.56±8.87 cm³ in diabetics with ANP with gallstones, 26.16±1.24 cm³ in diabetics with ANP with dysmotility 13.0±6.26 cm³ in diabetics with gallstones without ANP, 12.14±4.88 cm³ in normal diabetics and 13.60±5.95 cm³ in controls. The percentage contraction post fatty meal was calculated from these values and found to be 24.73±14.64% in diabetics with ANP with dysmotility, 26.38±17.04% in diabetics with ANP with dysmotility, 43.48±8.45% in diabetics with gallstones without ANP, 56.84±9.02% in normal diabetics and 57.64±9.92% in controls.

Conclusion: Incidence of gallbladder disease is much higher in type 2 diabetics (40%) as compared to normal healthy adults (4%). It was concluded that diabetics with ANP had significantly impaired gallbladder emptying. Poor control of diabetes, hypercholesterolemia and diabetic autonomic neuropathy are important risk factors for the development of gallbladder disease.

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin resistance, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and gastrointestinal system. Diabetes mellitus is one of the most common endocrine disorder. Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2002.¹ Diabetes mellitus is characterised by metabolic abnormalities and by long term complications involving eyes, kidneys nerves and blood vessels.² Digestive dysfunction is also a contributor to the morbidity of the

disease.³ Diabetic subjects are found to have increased incidence of gallstones.⁴ Inadequate emptying of gallbladder and increased volume has been reported.⁵ However contradictory results have been reported by some workers who observed no change in prevalence of gallbladder disease in diabetics.⁶

Hypomotility of gallbladder is suspected to be the result of autonomic neuropathy.⁷ Diabetic neuropathy is the most common neurological complication of diabetes and prevalence has been reported from < 5% to nearly 60% and even 100% if subclinical neuropathy is detected by electrophysiological studies.⁸ Autonomic involvement of gastrointestinal tract especially

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gallbladder may result in gall bladder atony resulting in poor contraction in response to fatty meals and higher incidence of gallstones.⁹ The present study was done to evaluate the incidence of gallbladder disorders and postprandial gallbladder volume and contraction in response to fatty meal in patients of type 2 diabetes mellitus and compare it with controls. It was also intended to find the incidence of autonomic neuropathy in these patients and correlate it with the presence of gallbladder disorders.

MATERIAL AND METHODS

This study was conducted on 50 diabetes mellitus type 2 patients and 25 age and sex matched controls enrolled from outpatient or inpatient services of Department of Medicine, Rajindra Hospital, Patiala. For the diagnosis and classification of diabetes criteria of fasting plasma glucose >126 mg/dl and postprandial glucose of >200 mg/dl as laid down by American Diabetes Association in 2010 was used. Type-2 diabetics with acute complications were excluded. After recording consent in writing detailed history, the age, sex, height, weight as per Performa were recorded.

Special attention was paid to gastrointestinal symptoms and autonomic dysfunction related symptoms. Haematological and biochemical investigation like Hb, TLC, DLC, FBS, blood urea, serum creatinine, serum cholesterol, urine examination and ECG were done. Autonomic neuropathy was assessed using noninvasive bedside tests like heart rate response to valsalva manoeuvre, heart rate variation during deep breathing, blood pressure response to handgrip exercise, immediate heart rate response to standing and blood pressure response to standing and analysed as per Ewing and Clarke's criteria.¹⁰ Ultrasonography of the abdomen was performed after 12 hours overnight fast using Gray Scale Real Time Scanner Siemens Sonoline L2 Ultrasound Unit. Various parameters observed were gallbladder volume and size, wall thickness, intraluminal mass and contraction in response to fatty meal. Gallbladder volume was calculated using ellipsoid method: $V = \frac{1}{6} (L \times W \times H)$

Where, L = Length of gallbladder W = Maximum width of gallbladder H = Maximum height of gallbladder Gallbladder motility was observed (a) By measuring fasting gallbladder volume by ellipsoid method (b) Post-meal gallbladder volume after giving 40 gm of fatty meal (butter) with bread to the patients. The measurements were done 60 minutes after fatty meal. The percentage of gallbladder contraction was calculated by the formula:

$$\frac{\text{Fasting GB volume} - \text{Post-fatty meal GB volume}}{\text{Fasting GB Volume}} \times 100$$

All the parameters were recorded as per Performa and analysed statistically by using students 't' test and chi square test.

RESULTS

Out of 50 patients of the study group 22 (44%) were males and 28(56%) were females with an age range of 25-70 years and a

mean of 50.98±11.63 years. Maximum numbers of patients were in the age group of 35-65 years. The average duration of diabetes was 5.25±4.43 years with a range of 0.5-22 years. Mean FBS level in the diabetic patients was 149.7±68.18 mg/dl with a range of 65-360 mg/dl and in the control group the FBS level was 96.24±14.82 mg/dl with a range of 75- 125 mg/dl. Mean FBS level in diabetics with gallstone disease was 179.65±71.55 mg/dl and in diabetics without gallbladder disease it was 129.73±58.90 mg/dl. (Table 1) Comparison of FBS levels in study group and controls.

Group	No. of Cases	Mean ± SD In mg/dl	P
DM+GBS vs DM-GBS	20	179.65 ± 71.55	<0.05*
	30	129.73 ± 58.90	
DM+GBS vs Controls	20	179.65 ± 71.55	<0.001**
	25	96.27 ± 14.82	
DM-GBS vs Controls	30	129.73 ± 58.90	<0.01*
	25	96.27 ± 14.82	

* Significant ** Highly Significant DM -Diabetes mellitus GBS- gallbladder stone/sludge

Incidence of gallbladder disease was higher in diabetics with poor sugar control.

The mean total serum cholesterol level in the study group was 166.6±30.82 mg/dl while in the control group it was 148.96±20.75 mg/dl. On further analysing the levels in diabetics with gallbladder disease it was found that mean total serum cholesterol level was 177.15±32.69 mg/dl. In diabetics without gallbladder disease the mean level was 159.56±27.88 mg/dl. It was concluded that total serum cholesterol levels positively correlated with the presence of gallbladder disease in diabetics. (Table 2)

Table 2: Comparison of serum cholesterol levels in study and control groups

Group	No. of cases	Mean ± SD	P
DM+GBS vs DM-GBS	20	177.15 ± 32.69	<0.05*
	30	159.56 ± 27.88	
DM+GBS vs Controls	20	177.15 ± 32.69	<0.01**
	25	148.96 ± 20.75	
DM-GBS vs Controls	30	159.56 ± 27.88	>0.05
	25	148.96 ± 20.75	

* Significant ** Highly Significant DM -Diabetes mellitus GBS- Gallbladder stone/sludge

There were 20 cases (40%) of gallbladder disease in the study group and only 1 case (4%) had gallbladder disease in the control group. It was concluded that the incidence of gallbladder disease was significantly more in diabetics.

The mean duration of diabetes in diabetics with gallbladder disease was found to be 7.77±5.0 years and 3.56±3.08 years in diabetics without gallbladder disease. Gallbladder disease positively correlated with the longer duration of diabetes.

The fasting gallbladder volume was 28.27±12.7 cm³ in diabetics with gallbladder disease, 27.79±7.63 cm³ in diabetics without gallbladder disease and 32.85±14.27 cm³ in controls. The postprandial volume was 18.75±8.51cm³ in diabetics with gallbladder disease, 12.14±4.88 cm³ in diabetics without gallbladder disease and 13.69±5.95 cm³ in controls. The mean

percentage contraction was calculated from the above values and was found to be 31.25±15.34% in diabetics with gallbladder disease, 56.84±9.02% in diabetics without gallbladder disease and 55.96±14.58% in controls. (Table 3)

Table 3: Comparison of Mean %age volume contraction in the study and control groups

Group	No. of Cases	Mean ± SD (%)	p
DM+GBS vs DM-GBS	20	31.52 ± 15.34	<0.001**
	30	56.84 ± 9.02	
DM+GBS vs Controls	20	31.52 ± 15.34	<0.001**
	25	55.96 ± 14.58	
DM-GBS vs Controls	30	56.84 ± 9.02	>0.05
	25	55.96 ± 14.58	

* Significant ** Highly Significant DM -Diabetes mellitus GBS- Gallbladder stone/sludge

It was concluded that there was reduced contractility post-fatty meal in diabetics with gallbladder disease as compared to the other two groups. Gallbladder wall thickness was measured and found to be 2.76± 1.19 mm in diabetics with gallbladder disease, 2.04±0.35 mm in diabetics without gallbladder disease and 2.06±0.47 mm in controls. It was concluded that gallbladder thickness positively correlated with the presence of gallbladder disease.

Autonomic neuropathy was assessed in the study and the control group and it was found that 13 diabetics (26%) had autonomic neuropathy while all the controls were negative for autonomic neuropathy. It was concluded that the incidence of autonomic neuropathy was 26% and was strongly correlated with the presence of diabetes. Of the 13 cases of autonomic neuropathy it was found that 5 had early parasympathetic dysfunction and 3 had definite parasympathetic dysfunction and 5 had combined sympathetic and parasympathetic dysfunction.

The fasting, postprandial gallbladder volume and percentage contraction were further analysed with respect to the presence or absence of autonomic neuropathy. Fasting gallbladder volume was 28.56+ 12.45 cm³ In diabetics with ANP with gallstones, 36.46±5.98 cm³ in diabetics with ANP with dysmotility, 24.34±14.65 cm³ in diabetics without ANP with gallstone 27.79±7 .63 cm³ in normal diabetics and 32.85±14.2 cm³ in controls. Although there was no statistical difference but it was found that ANP was positively correlated with higher fasting volumes.

Mean postprandial gallbladder volume was 20.56±8.87 cm³ in diabetics with ANP with gallstones, 26.16±1.24 cm³ in diabetics with ANP with dysmotility 13.0±6.26 cm³ in diabetics with gallstones without ANP, 12.14±4.88 cm³ in normal diabetics and 13.60±5.95 cm³ in controls. The percentage contraction post fatty meal was calculated from these values and found to be 24.73±14.64% in diabetics with ANP with GBS, 26.38±17 .04% in diabetics with ANP with dysmotility, 43.48±8.45% in diabetics with gallstones without ANP, 56.84±9.02% in normal diabetics and 57 .64±9.92% in controls. (Table: 4) It was concluded that diabetics with ANP had significantly impaired gallbladder emptying.

Table 4: Comparison of pre-prandial (fasting) and post-prandial gall bladder volume in study and control groups in relation to gallstone disease and autonomic neuropathy

Group	No. of Cases	Pre-prandial Mean ± SD in cm ³	Post-prandial Mean ± SD in cm ³	Mean %age contraction post fatty meal
DM+ANP-GBS	10	28.56± 12.45	20.56±8.87	24.73±14.64%
DM+ANP-Dys	3	36.46±5.98	26.16± 1.24	26.38±17.04%
DM-ANP+GBS	7	24.34± 14.65	13.0±6.26	43.48±8.45%
DM-ANP -GBS	30	27.79±7.63	12.14±4.88	56.84±9.02%
Control	25	32.85± 14.27	13.60±5.95	57.64±9.92%

DISCUSSION

Diabetes mellitus is a growing health care problem worldwide and is characterised by metabolic abnormalities and complications involving kidneys, nerves, blood vessels and the gastrointestinal tract.² Most severe impairment of gallbladder emptying was demonstrated in diabetics with autonomic neuropathy. The present study has been undertaken to evaluate the incidence of gallbladder disorders like gallstones, biliary sludge, wall thickness, fasting and postprandial gallbladder volume and contraction in response to fatty meal in patients of type 2 diabetes mellitus and compare it with controls. It was also intended to find the incidence of autonomic neuropathy in these patients and correlate it with the presence of gallbladder disorders.

Fbs & Cholesterol

The study showed that mean FBS and cholesterol levels were higher in diabetics with gallbladder disease than in diabetics without gallbladder disease and controls. The results were in accordance to the observations made by Yang *et al*¹¹ who concluded that gallbladder disease was related to poor blood sugar control.

Gallbladder Disease

The incidence of gallbladder disease was studied in both study and control group. It was found that 20 cases of the study group i.e. 40% had gallbladder disease. Of these, 17(34%) had gallstones, 20 (40%) had dysmotility and 17 cases (34%) had both i.e. a total of 20 cases. All the cases with gallstone disease had dysmotility also. In the control group only 1 case had gallstone disease i.e. 4% of the cases. Gallbladder disease was more prevalent in the diabetics than healthy controls. It was in concert with the findings of Raman *et al* [12] who found the incidence of gallstones in diabetics to be 32% and that in healthy controls to be 6.7%. The mean percentage gallbladder contraction was 31.25+15.34% in diabetics with gallbladder disease, 56.84±9.02 % in diabetics without gallbladder disease and in controls it was 55.96±14.58%. It was concluded that mean percentage contractility was significantly decreased in diabetics with gallbladder disease showing a strong association with the development of gallbladder disease.

According to Stone *et al*¹³ gallbladder emptying was lower in diabetics with gallbladder disease. In a study done by Raman *et al*¹² it was shown that percentage contraction of gallbladder was reduced in diabetes with gallbladder disease

(41.84±11.74%) as compared to controls (53.07±16.31 %) and diabetics without gallbladder disease (48.74±11.75%). Similar findings were produced by [Gaur et al.](#),⁷ [Pazzi et al.](#),¹⁴ [Yang et al.](#)¹¹ and [Kayacetin et al.](#)¹⁵ Thus the present study was clearly in concert with the above mentioned studies.

Autonomic Neuropathy

The incidence of autonomic neuropathy was studied using Ewing and Clarke criteria.¹⁰ 13 cases of the study group were found to have autonomic neuropathy and incidence worked out to be 26%. In the control group there was no case of autonomic neuropathy. On further studying the association of the autonomic neuropathy with gallstone disease and gallbladder dysmotility it was found that 10 patients who had autonomic neuropathy had gallstones i.e. 58.82% of all cases of gallstone disease had autonomic neuropathy and 3 had no gallstone but only dysmotility i.e. 9.09% of all cases without gallstone disease. There neuropathy was strongly associated with the presence of gallbladder disease especially were 7 diabetics who had gallstones without autonomic neuropathy Statistical analysis showed that autonomic gallstones. [Kayacetin et al.](#)¹⁶ had shown that gallbladder ejection fraction was significantly reduced in patients with autonomic neuropathy as compared to patients without autonomic neuropathy.

The statistical analysis showed that percentage contraction was significantly less in diabetics with ANP with gallstones and diabetics with ANP and dysmotility when compared to diabetics without ANP and controls. It was inferred that mean percentage contraction was significantly decreased in diabetics with ANP. [Stone et al.](#)¹³ demonstrated impaired gallbladder emptying in diabetics with autonomic neuropathy. [Pazzi et al.](#)¹⁴ in their study implicated visceral neuropathy to be the cause of reduced gallbladder motility. According to [Gaur et al.](#)⁷ gallbladder volumes were significantly larger in patients of diabetes mellitus and these values were significant in those with autonomic neuropathy.

It was reported by [Raman et al.](#)¹² that percentage contractility in diabetics with ANP was decreased (43.78±13.33%) as compared to controls (53.07±16.31%). However, [Keshavarzian et al.](#)¹⁶ reported that fasting and postprandial gallbladder volumes were comparable in diabetics and controls. Another study done by [Kayacetin et al.](#)¹⁵ showed that gallbladder ejection fraction was significantly reduced in patients with diabetic autonomic neuropathy (28.71±1.28%) as compared to diabetics without ANP (44.8±2.4%). Hence, our study was in concert with the results of above mentioned studies.

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