Original Research Paper

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Endocrinology

ULTRASONOGRAPHIC EVALUATION OF GALLBLADDER VOLUME AND ITS RELATION WITH AUTONOMIC NEUROPATHY IN DIABETIC PATIENTS OF JHARKHAND

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ABSTRACT **Introduction:** Diabetes mellitus is the most common endocrine disorder of humans characterized by metabolic abnormalities leading to long term complications. Neuropathy is one of the common complications of diabetes. Despite being a well-known consequence, autonomic neuropathy has received less attention than other microvascular sequelae. The involvement of both parasympathetic and sympathetic chains in autonomic neuropathy results in a variety of manifestations affecting various body organs. Gallbladder involvement in diabetic autonomic neuropathy is in the form of high incidence of gallstones and a significant increase in gallbladder volume with lack of symptoms of gallbladder disease. **Materials & Methods:** The study was conducted on 150 known diabetic patients and 150 age and sex matched controls. After detailed history, cardiac autonomic function is assessed by simple bedside tests and CAN score was assigned as per Ewing and Clarke's criteria. Ultrasound is used to assess the fasting gallbladder volume after 8 hours of fasting and postprandial gallbladder volume after fixed standard fatty meal. The results are analysed using MS-EXCEL, SPSS and MedCalc software. p value<0.05 was taken as statistically significant. **Results:** The fasting gallbladder volume in study group was 33.96 ± 15.19 as compared to 24.79 ± 9.96 in controls. Postprandial volume in study group was 24.01 ± 14.41 as compared to 16.28 ± 9.01 in controls. The difference was statistically significant. 120 patients in cases show some degree of autonomic neuropathy as compared to 65 patients in control group. Correlation of GBV with different parameters like HbA1c had Pearson's correlational coefficient (r) = 0.430, correlation with duration of diabetes had r = 0.391, correlation with CAN scoring had r = 0.757, correlation with microalbuminuria had r = 0.299. All results were statistically significant with p-value<0.05. However, correlation of GBV with age had (r) =0.0033, Correlation with BMI shows r=0.152 both results were statistically insignificant. Autonomic neuropathy was more prevalent in hypertensive subjects but result was statistically insignificant. **Conclusion:** The fasting and PP-gallbladder volume was higher in study subjects due to autonomic neuropathy. Correlation of GBV with glycemic control, duration of diabetes, Cardiac autonomic neuropathy shows a positive correlation, whereas correlation of autonomic neuropathy with Age, BMI and hypertension was statistically insignificant.

KEYWORDS :

Introduction

Diabetes mellitus is the most common endocrine disorder of humans characterized by metabolic abnormalities leading to long term complications involving kidneys, gastrointestinal tract, nerves and blood vessels, thereby causing morbidity and mortality.[1] It is broadly classified as Insulin dependent Diabetes Mellitus (IDDM) also known as type I DM and Non Insulin Dependent Diabetes Mellitus (NIDDM) also known as type II DM. The prevalence of type II is about 90%.[1] The current prevalence of diabetes in adults worldwide is 10.5%.[2]

Diabetes has steadily increased in India over the past three decades, with India accounting for a sizable portion of the global diabetes burden, primarily due to rising obesity and unhealthy lifestyles.

The findings from the 10th Edition of the IDF Diabetes Atlas[3], reports the age adjusted prevalence of diabetes in India to be 9.6% i.e. over 74 million adults in India of age group 20-79 years are living with diabetes which can alternatively be said as one in every 12 adults. This is expected to rise to 124 million by 2045 (prevalence= 10.4%). The number of people with diabetes in India is the second highest in the world, after China (141 million). The proportion of undiagnosed diabetes is third highest of the IDF Regions at 51.2% in south east asian (SEA) region.[55]

Jharkhand is the state in eastern India, where majority of the population is represented by the tribal and rural residents. As per NFHS-5[4] data diabetes status in scheduled tribe based on RBS values shows 90.7% population with below 140mg/dL.

A study conducted in 2011 by Anjana et al[5] on 16,607 individuals to study the prevalence of diabetes in urban and rural parts of India reported prevalence of 5.3% in Jharkhand in 2011.[5] A study conducted by Shafroz P et al.[6] in Hazaribagh district of Jharkhand on 375 individuals of age>20 years in 2019 (published in 2022) reports the prevalence to be 14.4% in urban area of Jharkhand based on fasting blood glucose levels.[6] The study also reported 11.2 % of pre diabetic population based of fasting blood glucose levels. This is in approximation to the results of Ranjit Mohan Anjana et al [7]nationwide study in 15 states and union territories of India in the year 2017 which reported the prevalence of 13.5% in urban population of Jharkhand.

Beginning years of diabetes is usually associated with asymptomatic hyperglycemia. Individuals with state of asymptomatic hyperglycemia being unaware of disease tend to develop complications at the time of diagnosis itself. Tribals are more frequently associated with disease ignorance and health unawareness which is attributed to limited health facilities in the area and lower literacy rates.

A state of chronic hyperglycemia resulting from diabetes leads to several macrovascular and microvascular complications.

Several studies over the time have shown increased prevalence of gallbladder diseases, impaired motility and stone formation in patients of Diabetes which can be attributed to cholecystomegaly and impaired gall bladder contraction mainly due to autonomic neuropathy.[8]

Despite being a well-known consequence, autonomic neuropathy has received less attention than other microvascular sequelae like retinopathy, nephropathy, and peripheral neuropathy.

The involvement of both parasympathetic and sympathetic chains in autonomic neuropathy results in a variety of manifestations affecting various body organs most pronounced of them are cardiovascular manifestation, Gastrointestinal (GI) manifestations & urinary bladder malfunction. Autonomic manifestations in the GI tract include gastropathies, nocturnal diarrhoea, oesophageal dysmotility, constipation, and gallbladder dysfunction, which are caused by reduced G.I. motility as a result of vagal neuropathy.[9-12]

Gallbladder involvement in diabetic autonomic neuropathy is in the form of high incidence of gallstones (GS) and a significant increase in gallbladder volume with lack of symptoms of gallbladder disease.[11-12]

The incidence of cholesterol GS has been reported to be 2–3 times higher in those with DM.[10] Additionally, they have demonstrated that individuals with numerous gallstones had considerably higher fasting GB volumes, while diabetics with autonomic neuropathy had a reduced gallbladder emptying rate.

Most studies on gall-bladder emptying have used either ultrasound or scintigraphy. Ultrasonographic studies in diabetics have reported different results.

Studies by Hahm JS & Park JY[13] in 1996, Singh S et al.[14] in 2006, and

in a recent study in 2022 Ikhuoriah et al [15] have found an increased fasting gall-bladder volume in diabetic patients compared with control subjects, whereas, Keshavarzian A and associates (1987) [16] and Wedmann B et al (1991)[17], have failed to find any significant difference. In a recent study Kumar DS & Kanakraj K [18] reported significant difference in postprandial gallbladder volume whereas difference in fasting gallbladder volume was statistically insignificant. The results have shown a significant difference in fasting gallbladder volume in some studies but not in others. These conflicting results could be due to a variety of factors possibly influencing gall-bladder motor functions, such as methodological differences (the dose and type of gall-bladder stimuli, the route of administration, and the meal composition), or heterogeneity in patients investigated (age, gender, body mass index, type of diabetes, presence of autonomic neuropathy, level of metabolic compensation).

Variety of techniques were devised in past to ascertain autonomic nervous system dysfunction. It was soon realised that autonomic neuropathy was much more common than previously thought.

Ultrasonography is an easy to perform radiological investigation, chosen as the modality to assess gall bladder volume as it is safe, inexpensive, less time consuming, accurate and doesn't lead to radiation exposure.

Although many studies have demonstrated the prevalence of autonomic neuropathy in diabetes, the study on population of Jharkhand is scanty. Moreover, among the available studies a large number of controversies exists that whether or not the changes in gallbladder physiology is significant enough to be attributed to diabetes.

This study was undertaken to evaluate the prevalence of gallbladder dysfunction secondary to autonomic neuropathy and postprandial gallbladder volume in response to standard egg yolk and high fat containing meal in tribal patients of type I and Type II diabetes mellitus and its comparison with healthy controls. This can further be used as marker of autonomic neuropathy in long standing disease greater than 5 years. The study has also determined the prevalence of gallstones in diabetics in comparison to normal subjects, and comparison of gallbladder volume and autonomic neuropathy to various other factors like duration of diabetes, glycemic control, age, gender, BMI and presence of other microvascular complications.

Materials and Methods

Study population: Patients with Diabetes Mellitus who were admitted in Department of Medicine, Rajendra Institute of Medical Sciences, a tertiary care centre in Ranchi, and who were the permanent residents of Jharkhand were taken for study considering the inclusion and exclusion criteria.

Selection of study group

Study group consist of 150 diabetic patients with definite diagnosis of Diabetes Mellitus

Inclusion criteria:

1. Patients giving written and duly signed informed consent.
2. Adults more than 18 years of age.
3. Diabetic patients known to have disease for ≥ 5 years.
4. No evidence of gastrointestinal or hepatobiliary disease

Exclusion criteria:

1. Patients not willing to participate in the study
2. Pediatric population ≤18 years old.
3. Pregnant females.
4. Known alcoholics.
5. Patients with history of stroke.
6. Patient taking any drug which can interfere with autonomic functions.
7. Patients with history of cardiac arrhythmias.
8. Patient with strict vegetarian diet.

Selection of control group:

Control group consisting of age, sex and BMI matched 150 volunteers from hospital without any known diabetes, gastrointestinal, renal, and cardiac disease were recruited after taking duly signed informed consent.

The selected patients were studied in detail with history and physical examination.

Study design: Hospital based Observational Case-Control study.
Study duration: 18 months.

METHODOLOGY

Each patient selected for study, fulfilling inclusion and exclusion criteria were explained the whole procedure and study method and a duly signed informed consent was obtained for their participation. Patients were thoroughly interviewed based on pre formed questionnaire Performa.

1) A complete basic detail of the patient (name, age, sex, address etc.) was noted down.
2) Detailed history taking of each and every patient was done. It included: -

- Total duration of diabetes and complete treatment history. The compliance for the present treatment was also enquired.
- Detailed personal history regarding smoking, alcoholism, any other drug was noted.
- Past history:- syncope, drugs, blood transfusions, hypertension, leprosy thyroid disorder, coronary artery disease, cardiac arrhythmia, abdominal surgeries etc were recorded.
- A detailed history was recorded with special preference to symptoms of autonomic neuropathy like nocturnal diarrhoea or constipation, hypoglycaemic unawareness, sphincter disturbances, orthostatic hypotension, sudomotor and pilomotor disturbances, and erectile dysfunction and parasthesias.

3) Thorough clinical examination of each and every patient was done. This included:-

- Anthropometric parameters of obesity as per WHO recommendations like standing height, weight, BMI, Waist-Hip ratio, sphygmomanometer auscultatory arterial blood pressure, resting 12-lead electrocardiogram.
- A complete general examination of all the organ systems.

AUTONOMIC FUNCTION TESTS

Cardiac autonomic neuropathy in diabetic patients was assessed clinically by using simple non-invasive cardiovascular bedside tests, which included heart rate variation during squatting, heart rate variation during deep breathing, immediate heart rate response to standing, blood pressure response to standing and blood pressure response to sustained handgrip.

The following autonomic function tests were performed, of the five tests; the first two tests were used for sympathetic and later three for parasympathetic nervous system.

Blood Pressure response to standing: Blood pressure was recorded in the right upper arm by sphygmomanometer in supine position at rest and again recorded 1 minute after standing. The postural fall in systolic blood pressure was taken as a difference between systolic pressure in supine and systolic pressure on 1 min. after standing.

Normal: ≤ 10 mmHg. Borderline: 11 – 20 mmHg. Abnormal: ≥ 30 mmHg.

Blood Pressure response to sustained handgrip: Resting systolic blood pressure was recorded. Subjects were asked to maintain handgrip in other arm at 30% of maximum voluntary pressure for up to 5 minutes. Systolic pressure was recorded every minute. The difference between the resting systolic pressure and maximum systolic pressure during sustained handgrip was considered for the interpretation.

Normal: ≥ 16 mmHg. Borderline: 11–15 mmHg. Abnormal: ≤ 10 mmHg

Heart rate response to standing: The ECG limb leads were attached and ECG was recorded in lead II. Subject/patient stands from supine position as quickly as possible. The 30:15 ratio i.e. ratio of longest R-R interval around 30th beat after standing to shortest R-R interval about 15th beat after standing were considered.

Normal: ≥ 1.04. Borderline: 1.01-1.04. Abnormal: ≤ 1.00

Heart rate response to deep breathing: With subject sitting, ECG was recorded in lead II throughout the period of deep breathing. Subject breathe deeply and evenly at 6 breaths per minute (5 sec. in, 5 sec. out) for 3 cycles (30 sec.). The onset of inspiration and expiration were marked on ECG paper. The maximum and minimum R-R intervals were measured during expiration and inspiration in each cycle. The heart rate difference during each cycle was measured and average of the 3 differences was considered.

Normal: ≥15 beats / min. Borderline: 11–14 beats / min. Abnormal: ≤10 beats/min.

Heart rate response to Valsalva manoeuvre: The quantitative Valsalva manoeuvre was performed by blowing with open glottis into a mouthpiece connected to mercury column of a sphygmomanometer. Subjects were asked to maintain 40–50mmHg. Pressure for 15 sec. The ECG was recorded 15 sec, during and 30 sec. after the manoeuvre. Valsalva ratio was calculated by using the following formula.

$$\text{Valsalva ratio} = \frac{\text{Longest R R interval after manoeuvre}}{\text{Shortest R R interval during manoeuvre}}$$

Normal: ≥ 1.21, Borderline: 1.11 – 1.20: Abnormal: ≤ 1.1

Ewing's and Clarke's protocol for assessment of Cardiac Autonomic Neuropathy Score (CAN) [19]

Name of tests	Normal (score 0)	Borderline (score 0.5)	Abnormal (score 1)
Heart rate response to valsalva manoeuvre (VR)	≥ 1.21	1.11 – 1.20	≤ 1.10
Heart Rate response to Deep breathing (DBD)	≥ 15 beats/ min	11- 14 beats/ min	≤ 10 beats/ min
Heart rate response to standing (PTI)	≥1.04	1.01- 1.03	≤ 1.00
Blood pressure response to standing (Fall in SBP)	≤10 mm of Hg	11-30 mm of Hg	≥30 mm of Hg
Blood pressure response to sustained hand grip (SHG)	≥16 mm of Hg	11-15 mm of Hg	≤10 mm of Hg

RESULTS:[19]

Normal: All tests normal, or one borderline result.

Mildly abnormal: One of the three heart rate tests abnormal, or 2 borderline (mild)

Definitely abnormal: Two or more of the heart rate tests abnormal (moderate) Severely abnormal: Two or more of the heart rate tests abnormal, plus one or both of the BP tests abnormal, or both borderline (severe).

Procedural Outline of USG

An ultrasonographic evaluation of fasting gallbladder volume and postprandial gallbladder volume was done in all the subjects using a 3.5 or 5 MHz transducer. The greatest length (L), greatest transverse width (W), and antero-posterior (H) dimensions and presence of gallstones were recorded. Gallbladder volume was obtained after a standard breakfast consisting of two boiled eggs, 200 ml milk 100 gm toast and 1 medium sized banana (containing 695 Kcal and 20.5gm fat) and labelled postprandial volume. All the sonographic measurements were recorded by a single, experienced observer.

The gall bladder volume was calculated using the ellipsoid formula.

STATISTICALANALYSIS

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences IBM SPSS version 28.0, MedCalc for windows version 20.120. Categorical variables were presented in number and percentage (%) and continuous variables will be presented as mean±SD and median.

Statistical tests like independent student t test parametric, non parametric, chi square test, Z-test, F-test for variance were applied to check the statistical significance. Pearson's correlation coefficient was calculated for correlation of variables. The p-value of <0.05 was considered statistically significant.

Observations and Results

Age distribution of patients studied

The youngest patient studied was, 20 year old and oldest patient was 95 year old. The mean age of diabetics in study group was 53.20 ± 15.82 years & in controls 55.93 ± 15.27 years. Majority of the patients as well as controls were between the ages of 40 – 69yrs.

Samples were age matched with p=0.129 (Insignificant)

Gender distribution of patients studied

The study sample includes 84 males and 66 females in study group and 85 males and 65 females in control group. Both sexes were of equally distributed in cases & controls groups.

Table 1: Comparison of Age, BMI and WHR between controls and Cases

Variables	Study Group	Control Group	p-value
Age	53.20 ± 15.82	55.93 ± 15.27	0.129 (NS)
BMI	23.86 ± 3.03	23.75 ± 2.53	0.733 (NS)
WHR	0.872 ± 0.093	0.863 ± 0.071	0.346 (NS)

There was no significant difference between the demographic parameters with respect to Age, BMI and WHR.

Obesity, a confounding factor in Gall bladder volume is equally distributed over cases and control groups.

Table 2: Mean gall bladder volume in study and control groups

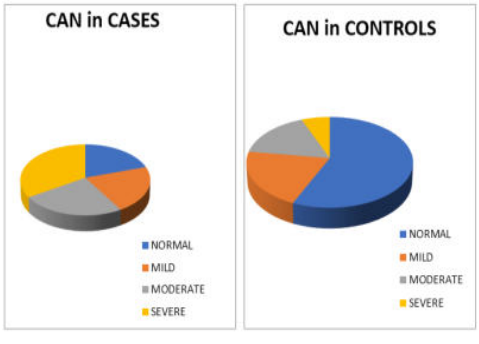
Gall bladder volume	Control	Cases
Fasting	24.79 ± 9.96	33.96 ± 15.19
Postprandial	16.28 ± 9.01	24.01 ± 14.41

- Gall bladder volume was significantly higher in fasting state in Cases (diabetics) compared to controls. The difference is statically significant with p value < 0.001.
- Gall bladder volume was significantly higher in postprandial state in Cases (diabetics) compared to controls. The difference is statically significant with p value < 0.001

Table 3: Prevalence of Cardiac Autonomic Neuropathy (CAN) in study & control groups

CAN	CASES		CONTROLS	
	Number	Percentage	Number	Percentage
Normal	30	20	85	56.67
Mild	32	21.33	31	20.67
Moderate	37	24.67	25	16.66
Severe	51	34	09	6.00
Total	150	100	150	100

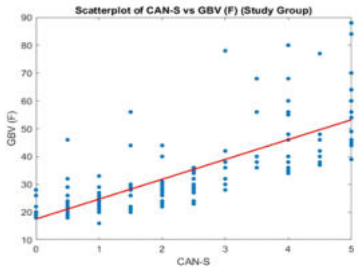
In this study, Cardiac autonomic neuropathy was more prevalent in cases as compared to controls. Among cases 80% of patients were reported to have some degree of autonomic neuropathy in which 21.33% mild, 24.67% moderate and 34% having severe autonomic neuropathy. However in control group only 43.33% individuals were reported to have autonomic neuropathy in which 20.67% mild, 16.66% moderate and only 6% having severe autonomic neuropathy.



Graph 1: Pie-chart showing cardiac autonomic neuropathy among cases and control

CORRELATION OF FASTING GALLBLADDER VOLUME WITH CARDIAC AUTONOMIC NEUROPATHY SCORING (CAN-S)

In our study, Fasting gallbladder volume was correlated with cardiac autonomic neuropathy scoring (Ewings Score).[19] The Pearson's correlation coefficient in study group was 0.757 with p value <0.0001 which is statistically significant.



Graph 2: Scatter diagram of Cardiac autonomic neuropathy scoring Vs Fasting Gallbladder volume (STUDY GROUP)

Table 4: Prevalence of gallstone and gender wise distribution

GB STONE	Cases		Controls	
	Number	Percentage	Number	Percentage
Males	7	8.33%	4	4.7%
Females	15	22.72%	5	7.69%
Total	22	14.6	9	6%

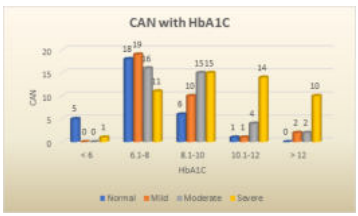
22 Patients (14.6%) among cases were suffering from gallstone, as compared to 9(6%) individuals among controls. There is increased prevalence of gallstone disease among cases (diabetics) and the difference is statistically significant with p-value = 0.0238.

The number of female patients having gallstone was in excess among both the cases and the controls. Among study group 15 females (22.72%) were suffering gallstone disease in contrast to 7 males (8.33%). The difference between males and females in study group was statistically significant with p-value=0.025. Among controls 5 females (7.69%) were reported to suffer gallstone disease in contrast to 4 males (4.7%). Females are reported to have high prevalence of gallstone till the age of 50 probably due to hormonal influence on bile composition and gallbladder motility.

GLYCEMIC CONTROL

Table 5: Comparison of CAN with HbA1C

HbA C	Cardiac Autonomic Neuropathy (CAN)			
	Normal	Mild	Moderate	Severe
<6	05	00	00	01
6.1-8	18	19	16	11
8.1-10	06	10	15	15
10.1-12	01	01	04	14
>12	00	02	02	10



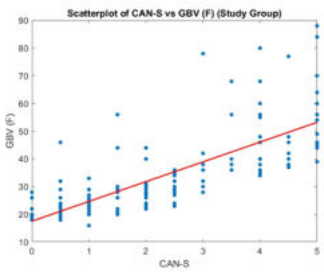
Graph 3: Bar Graph representation of cardiac autonomic neuropathy with HbA1c

In this study, patients with lower HbA1c levels have lesser degree of autonomic neuropathy whereas patients with higher HbA1c have greater severity of autonomic neuropathy. Maximum patients with HbA1c > 8 have severe grade of autonomic neuropathy.

Among the diabetic patients who have CAN the mean HbA1c level was 8.97 ± 2.02, whereas in diabetic patients who did not developed CAN the mean HbA1c level was 7.25 ± 1.09. The comparison of two means shows p-value< 0.0001 which is statistically significant.

Correlation between HbA1c levels with CAN-scoring shows correlation coefficient r=0.43 with p-value<0.0001 which is statistically significant.

Graph 4: Scatter diagram of Cardiac autonomic neuropathy scoring Vs Fasting Gallbladder volume (STUDY GROUP)

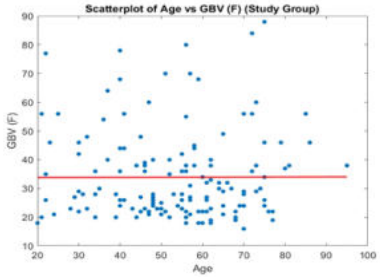


GALLBLADDER VOLUME

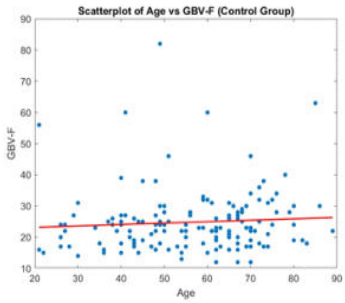
Table 6: Comparison of Gallbladder volume with Age

AGE (years)	Fasting GB volume			Postprandial GB volume		
	Study Group	Control Group	p-Value	Study Group	Control Group	p-Value
20-39	35.20± 15.09	22.25± 9.16	0.0013 (S)	24.68± 14.48	14.65± 7.62	0.0068 (S)
40-59	34.03± 15.63	25.25± 10.93	0.0004 (S)	24.43± 15.13	16.80± 7.62	0.0016 (S)
60-79	32.20± 15.15	24.62± 8.47	0.001 (S)	22.32± 13.99	16.00± 7.82	0.0031 (S)
≥80	43.00± 8.12	28.12± 14.86	0.066 (NS)	31.40± 6.02	18.62± 12.42	0.057 (NS)

In this study, comparison of fasting as well as postprandial gallbladder volume in individuals below 80 years of age in study and control group shows significant difference with p-value<0.001. However in subjects of 80 years and above age group the difference in gallbladder volume among study and control groups was statistically insignificant with p-value=0.066 in fasting and p-value =0.057 in postprandial state respectively.



Graph 5: Scatter diagram showing correlation of gallbladder volume with age of patients in study group

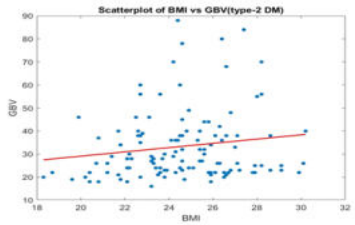


Graph 6: Scatter diagram showing correlation of gallbladder volume with age of subjects in control group

correlation of fasting gallbladder volume with age among control group subjects was statistically insignificant with p-value 0.398 and Pearson's correlational coefficient r=0.069.

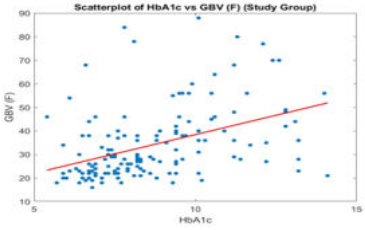
COMPARISON OF FASTING GALLBLADDER VOLUME WITH BMI

In our study, correlation of BMI with gall bladder volume in patients with type II diabetes mellitus shows positive correlation with Pearson's correlation coefficient r=0.152. However, the results are statistically insignificant with p-value = 0.0965.



Graph 7: Scatter plot correlation of Fasting gallbladder volume with BMI

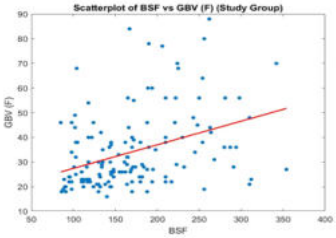
CORRELATION OF FASTING GALLBLADDER VOLUME WITH HbA1c



Graph 8: Correlation of Fasting gallbladder volume with HbA1c in (STUDY GROUP)

In this study, correlation of Fasting Gallbladder volume with HbA1c in study group was positively correlated with Pearson's correlation coefficient 0.430 and p-value <0.0001 which is statistically significant.

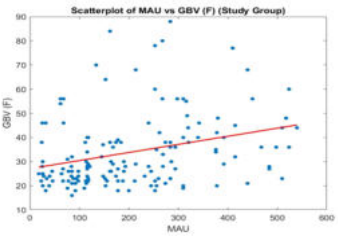
CORRELATION OF FASTING GALLBLADDER VOLUME WITH FASTING BLOOD SUGAR (BSF)



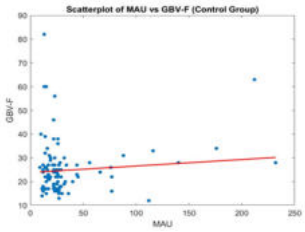
Graph 9: scatter diagram of fasting Blood sugar Vs Fasting Gallbladder volume (STUDY GROUP)

In our study, correlation of fasting gallbladder volume with fasting blood sugar levels among diabetics is positively correlated with Pearson's correlation coefficient r =0.382 with p-value<0.0001 which is statistically significant.

COMPARISON OF FASTING GALLBLADDER VOLUME WITH MICROALBUMINURIA (MAU)



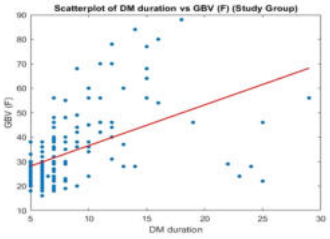
Graph 10: scatter diagram of Microalbuminuria Vs Fasting Gallbladder volume (STUDY GROUP)



Graph 11: scatter diagram of Microalbuminuria Vs Fasting Gallbladder volume (CONTROL GROUP)

In our study, correlation of Microalbuminuria with Fasting gallbladder volume in study group was positively correlated with Pearson's correlation coefficient r=0.299 with p-value = 0.0002 which is statistically significant, whereas comparison in control group was positively correlated with Pearson's correlation coefficient r =0.110. However, p-value was 0.176 which was statistically insignificant.

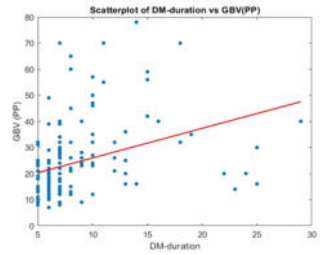
CORRELATION OF FASTING GALLBLADDER VOLUME WITH DURATION OF DIABETES



Graph 12: Scatter diagram of Fasting Gallbladder volume Vs Duration of Diabetes Mellitus (STUDY GROUP)

In this study, fasting gallbladder volume was correlated with total duration of diabetes mellitus patient was suffering. The result was positively correlated with Pearson's correlation coefficient r=0.391, the correlation was statistically significant with p-value <0.001.(HS)

Postprandial gallbladder volume was correlated with total duration of diabetes mellitus patient was suffering. The result was positively correlated with Pearson's correlation coefficient r 0.350, the correlation was statistically significant with p-value <0.001 (HS).



Graph 13: Scatter diagram of Postprandial Gallbladder volume Vs Duration of Diabetes Mellitus (STUDY GROUP)

Table 8: Strength of Association: ODDS RATIO

	CAN Present	CAN absent
Study group	120	30
Control group	65	85

$$\text{Odds Ratio} = \frac{AD}{BC} = 5.23.$$

In present study odds ratio was 5.23, meaning diabetics have 5.23 times higher risk of developing autonomic neuropathy as compared to non diabetics.

Discussion

The present study was done on 150 cases and 150 age, sex and BMI matched controls. The gall bladder volume in fasting and postprandial state was measured and compared to various other parameters like age, gender, BMI, microalbuminuria and duration of diabetes. The data has been analysed and compared with various studies in literature.

The comparison of difference in age and gender in control groups with cases is statistically insignificant. This shows that the controls are matched with cases in terms of age and sex.

Obesity is reflected by BMI and WHR in present study. Obesity can influence gallbladder volume as shown in study by Nushrat Jahan Tahnia et al[20], Kishore C and Priya R[21] and Jagdeesh KS and Patil M[22] on diabetic neuropathy. Obesity acts as a confounding factor in estimation of gallbladder volume. In present study effect of

confounding factor is nullified by selection of control group matched with cases in terms of BMI and WHR.

The fasting gallbladder volume in cases was 33.96 ± 15.1 ml and in control was 24.79 ± 9.96 ml. The result shows statistically significant difference between cases and controls with p value <0.001. Similar results were obtained in previous studies by Tahnia NJ et al[20], Jagdeesh KS[22], Sudheer R & Basawaraj[23]and Ikhouria et al.[15]

GB volume	Jagdeesh KS (2020)	Sudheer R (2021)	Tahnia NJ (2021)	Ikhouria et al.(2022)	Present Study
No of cases	90	100	148	120	150
GBV in cases	33.33±6.42	24.7±10.5	27.57±1.08	34.51±3.16	33.96±15.1
GBV in controls	N/A	17.8±4.0	14.55±3.05	27.17±1.25	24.79±9.96

The postprandial (PP) gallbladder volume was compared between cases and controls. In present study, PP gallbladder volume in diabetics was 24.01±14.41 and in controls was 16.28 ± 9.01 with difference being statistically significant p value< 0.001. The results were similar to the findings of Garjesh S Rai et al[24] , Jagdeesh KS[22] and Kumar DS & kanakraj K.[23]

In our study, 80% of the study subjects were reported to have some degree of autonomic neuropathy. Maser RE et al[25] in a meta-analysis including 15 studies from 1966 to 2001 reported prevalence rates of CAN between 1 and 90%.[190] Dimitropoulos et al[26] reported a prevalence of CAN that varies between 1- 90% in patients with T1DM and 20–70% in patients with T2DM.[191] Ziegler et al.[27] in a multicenter study reported that the prevalence of CAN in T1DM and T2DM patients as 25.3% and 34.3%, respectively.

In present study, cardiac autonomic neuropathy was more prevalent in cases as compared to controls. Among cases 80% of patients were reported to have some degree of autonomic neuropathy, results were similar to other studies Maser RE et al[25] and Dimitropoulos et al.[26]

Dimitropoulos et al[26] also reported positive correlation of autonomic neuropathy with CAN scoring. The same is shown in present study in positive correlation of fasting gallbladder volume with cardiac autonomic neuropathy scoring (Ewings and Clarke's Score).[19] The Pearson's correlation coefficient in study group was 0.757 with p value<0.0001 which is statistically significant. The coexistence of cardiac autonomic neuropathy among cases confirms our diagnosis of autonomic neuropathy and cholecystoparesis due to neuropathy. It shows that increased gallbladder volume is due to neuropathy and not due to any other possible causes.

In our study, 22 Patients were suffering from gallstone among cases whereas 9 patients among controls were having gallstone. Female predominance was seen in both the groups. There was increased prevalence of gallstone disease among cases (diabetics) and the difference was statistically significant with p-value=0.0238. The results were similar to various other studies mentioned below in table with incidence in range of 9.2% to 32%. However, the incidence of gallstone is comparatively low as compared to majority of studies. Environmental and dietary factors or demographic variation may contribute to variations in GBD burden from one geographical location to another. Or this can be due to the selection bias in data collection as study group patients were selected from medicine wards only and most patient with gallstones gets admitted in surgery department. However, the higher prevalence of GB stone in females as reported in this study is in concert with previous studies of Pagliarulo et al[10], Raman PG et al [28], Saxena et al [29], and Elmehdawiet et al.[30]

Study Name	Gallstone in cases	Gallstone in controls
Raman PG et al[28] (2002)	32%	6%
Chhabra A et al[31](2013)	34%	4%
Agunloye AM et al[32] (2013)	17.5%	N/A
Kumar DS, Kanakaraj K[23] (2021)	32%	16%
Ikhouria et al.[15] (2022)	9.2%	00
Present study	14.6%	6%

In this study, Mean HbA1c among cases was 8.62±1.99 as compared to 5.00±0.35 among controls.

Maximum patients with HbA1c>8 have severe grade of autonomic neuropathy. Among the diabetic patients who have CAN the mean HbA1c level was 8.97±2.02, whereas in diabetic patients who did not developed CAN the mean HbA1c level was 7.25±1.09. The difference shows p-value< 0.0001 which is statistically significant. Correlation between HbA1c levels with CAN-scoring shows correlation coefficient r=0.43 with p-value<0.0001 which is statistically significant. This shows that there is higher chance of development of autonomic neuropathy with uncontrolled diabetes.

Kumar et al.[33] reported positive correlation between HbA1c and gallbladder dysfunction with p-value 0.03 and Pearson's correlation coefficient r=0.081. The results in present study were similar to Kumar A et al study.

In our study, correlation of fasting gallbladder volume with fasting blood sugar levels among diabetics was positively correlated with Pearson's correlation coefficient r=0.382 with p-value<0.0001 which is statistically significant. The results show positive correlation between poor glycemic control and development of autonomic neuropathy. However, the correlation (r=0.382) is weaker than HbA1c (r=0.43), which is because HbA1c better predicts the glycemic control over longer duration.

Autonomic neuropathy also develops with advancing age. Comparison of fasting as well as postprandial gallbladder volume in individuals <80 years of age in study and control group shows significant difference with p-value<0.001. However in subjects 80 years and above age group the difference in gallbladder volume among study and control groups was statistically insignificant. Correlation of fasting gallbladder volume with age of patient was statistically insignificant. Results were in concert with the previous studies by Ikhouria et al.[15], Raman PG et al[28], Tahnia NJ et al[20], and Mohammed et al.[34]

Agrawal AK et al[35] and Tahnia NJ et al[20] in their studies have reported a positive correlation of fasting gallbladder volume with BMI. The correlation however was insignificant in Agrawal AK study. In present study, correlation of BMI with gall bladder volume in patients with type II diabetes mellitus, shows positive correlation with Pearson's correlation coefficient r=0.152. However, the results are statistically insignificant with p-value = 0.0965. This study is in accordance with general trend of decreasing gallbladder motility with increasing obesity. The results are in accordance with previous studies. 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.[24]

Agarwal AK et al[35] in 2004 reported a positive correlation between microalbuminuria and gallbladder volume and autonomic neuropathy. However, their result was statistically insignificant. In present study, correlation of microalbuminuria with fasting gallbladder volume in study group was positively correlated with Pearson's correlation coefficient r=0.299 with p-value=0.0002 which is statistically significant, whereas comparison in control group was positively correlated with Pearson's correlation coefficient r=0.110. However, p-value was 0.176 which was statistically insignificant.

This show, all the complications of diabetes develops simultaneously. The results are not surprising as the mechanism and pathogenesis of microvascular complications remains same. Patient having one complication is likely to develop other complications as well. Patient having autonomic neuropathy are more likely to develop nephropathy and vice versa. This has a great clinical significance in educating the patient about other complication and early prediction and detection of hazardous complications.

Agrawal AK et al[35] and kishore C & Priya R[21] in their study reported positive correlation of gallbladder disease with increasing duration of diabetes. Garjesh S Rai et al[24] reported positive correlation of gallbladder volume with duration of diabetes with chi-square correlation coefficient 0.379. However, correlation in both the studies was statistically insignificant. Chhabra et al[31] reported increasing incidence of gallbladder disease with increasing duration of diabetes.

In present study, fasting gallbladder volume as well as postprandial gallbladder volume was positively correlated with total duration of disease. Agunloye AM [32] reported positive correlation of gallstone disease due to cholecystoparesis with duration of diabetes. In the present study, result was positively correlated. This is in accordance with previous studies and shows the increasing chances of autonomic neuropathy with increasing duration of diabetes.

The odds ratio of developing autonomic neuropathy among cases and control happens to be 5.23, which means, the risk of developing autonomic neuropathy in diabetes is 5.23 times more than the normal individual.

CONCLUSION

Diabetes Mellitus has many short term and long term complications. Autonomic neuropathy is one of the major complications that can involve cardiovascular system, gastrointestinal system, urogenital system which leads to poor quality of life with life threatening complications like postural hypotension, unawareness to hypoglycaemia, and silent ischemia. The prevalence of autonomic neuropathy is very common, reported 80% in present study and correlates with factors namely obesity (body Mass Index), glycemic control (HbA1c and Fasting Blood Sugar), duration of diabetes and simultaneous progression of other microvascular complications like nephropathy. Many of the factors are modifiable risk factors and careful disease awareness and better compliance to treatment can prevent or delay development of major complications.

Cardiac autonomic neuropathy can be used as the screening test in estimation of autonomic neuropathy, as it is easy to perform bedside and yields nearly accurate results. In present study, cardiac autonomic neuropathy scoring and grading correlated significantly with the ultrasonographic findings of increased gallbladder volume.

This study reports a significantly higher fasting and postprandial gallbladder volume in diabetics as compared to control group which is a result of gallbladder motor paresis secondary to autonomic neuropathy. The diabetics had significantly higher prevalence of gallstone disease as compared to controls. Thus, diabetes is a risk factor for gallbladder diseases and cholecystoparesis can lead to bile stasis, cholecystitis, and gallstone. A regular screening is necessary for early diagnosis and early treatment of diseases like gallstones.

Autonomic neuropathy is a common complication of diabetes mellitus that develop with poor glycemic control over long term. Patients should be screened for autonomic neuropathy routinely to impart a better quality of life.

LIMITATIONS OF STUDY

The study was conducted with limited resources and limited time. Therefore few inevitable limitations are present in the study. The limitations are:-

I. The gallbladder volume was calculated using ultrasonography due to unavailability of scintigraphy. Scintigraphy is considered gold standard for measurement of gallbladder volume. The research should be repeated with scintigraphy to minimise the error.

II. Only gallbladder volume is taken into account during the study. Considering gallbladder ejection fraction in the study could be a better idea to establish the etiology of cholecystomegaly.

III. Cardiac autonomic function test was used for assessment for autonomic neuropathy. MIBG scan is considered gold standard. Research should be carried out further with MIBG scan for accurate results.

IV. To establish the temporal relation of diabetes and effects of autonomic neuropathy the scope of case control study is limited. A large population based prospective cohort study is required.

V. This study is a single hospital based case control study. The study sample doesn't reflect the exact population. Further research with possibly large sample size and sample which can mirror the population, needs to be done.

VI. There were fewer study subjects with type I diabetes. A fair selection and inclusion of large number of type I DM study subjects is required for better comparison and a definite conclusion.

VII. In our study, blinding was not done, therefore there is a possibility of a large number of bias. We recommend a further research with triple blinding in consideration for fair results.

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