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# Study of Gallbladder contractile function by Ultrasonography in patients of type 2 Diabetes Mellitus and it's correlation with HbA1c and Diabetic Neuropathy

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## ABSTRACT

**Background:** Type 2 diabetes mellitus is commonest endocrine disorder with a continuous rising prevalence and its complications. 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. [1] Diabetic autonomic neuropathy gives rise to varied manifestations in the gastrointestinal tract i.e. gastropathies, nocturnal diarrhoea, oesophageal dysmotility, constipation and gallbladder dysfunction, being consequence of vagal neuropathy leading to reduced G.I. motility .Gall bladder is one of the commonly affected organs in chronic diabetics, most probably due to autonomic neuropathy which adversely affects gall bladder contractile function. **Methods:** This institution based case-control, cross sectional, observational study had been performed among 100 Cases (Patient suffering from Diabetes Mellitus type 2) and 50 controls (non-diabetic) will form the sample randomly selected from of Department of Medicine, Santosh Medical College &Hospital, Ghaziabad, UP. All patients and volunteers had undergone abdominal ultrasonography for any existing hepato-biliary pathology and to measure fasting and post fatty meal gall bladder volume and HbA1c and FBS levels. **Results:** It was seen that the FGBV (Fasting Gall bladder volume) was significantly higher in diabetic patients with neuropathy than in Non-diabetic.. The mean percentage gallbladder contraction was 20.62+12.86 % in diabetics and in controls it was 25.89+12.53%.The incidence of autonomic neuropathy was studied using Ewing and Clarke criteria, 55 cases of the study group were found to have autonomic neuropathy. In the control group there was no case of autonomic neuropathy. The statistical analysis showed impaired gallbladder emptying in diabetics with autonomic neuropathy. Gall bladder dysfunction shows moderate positive correlation with HbA1c levels. **Conclusion:** This study concludes that there are high incidence of gall bladder contractile dysfunction in diabetic patients as compared to healthy controls. Further gall bladder dysfunction shows moderate positive correlation with HbA1c levels. Also we conclude that contractile dysfunction is more severe in Diabetics with cardiac autonomic neuropathy. Therefore it is suggested that diabetic patients with autonomic dysfunction should be carefully evaluated for gall bladder dysfunction by non-invasive method like ultrasonography so as to prevent future complication related to gall bladder like cholecystomegaly, cholelithiasis, cholecystitis etc.

***Keywords:*** Fasting gall bladder volume, Ultrasonography, Autonomic neuropathy, Ewing and Clarke criteria.

## INTRODUCTION

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.[1] Diabetic autonomic neuropathy gives rise to varied manifestations in the gastrointestinal tract i.e. gastropathies, nocturnal diarrhoea, oesophageal dysmotility, constipation and gallbladder dysfunction, being consequence of vagal neuropathy leading to reduced G.I. Motility. Gallbladder involvement in diabetic autonomic neuropathy is in the form of high incidence of gall bladder stones and a significant increase in gall bladder volume, decreased ejection fraction, with poor concentration and lack of symptoms of gallbladder disease.[2-3]

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.

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Various studies point towards an increased prevalence of gall bladder disease in diabetics.[4-6] This has been attributed to cholecystomegaly and impaired gall bladder contraction, mainly due to autonomic neuropathy seen in diabetics. Previous studies done to estimate gall bladder volumes and ejection fraction in diabetics show cholecystomegaly and decreased ejection fraction in comparison with the general population. However, not many such studies have been done in the North Indian population.

Ultrasonography is a very cost effective, safe, cheap and easy to perform imaging modality to assess gall bladder volume, though being highly operator dependant which can give consistent and accurate results. It is therefore both intriguing and necessary to study and compare the differences in Gall Bladder volume and ejection fractions via ultrasonography among patients suffering from Diabetes Mellitus type 2 and the general population.

**Aims and Objectives**

1. To estimate Gall bladder volume and ejection fraction in Type 2 Diabetics and in controls.
2. Correlation of Gall Bladder contractile dysfunction with HbA1c and Diabetic Neuropathy.
3. Comparison of gall bladder volume and ejection fraction in patients with/ without autonomic neuropathy as well as controls.

## MATERIALS AND METHODS

The present case-control, cross sectional, observational study was conducted on 100 diabetic patients enrolled from the diabetes clinic of the Department of Medicine, Santosh Medical College, Ghaziabad, U.P, 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 hrs of ingestion of standardised 75 gm glucose. An informed consent was taken from all the subjects in the study and control groups. Selected patients cases as well as controls were referred to the department of Radiology Santosh Medical College for sonological evaluation of Gall bladder after their informed consent 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**

**Cases:** Patients with pre-existing / newly diagnosed DMT2

**Controls:** Patients who are age and sex matched with case group in all variables except DMT2

**Criteria common to both cases and controls:**

-Non-obese patients (BMI <35)

-Non pregnant females

**Exclusion criterion**

1. Morbid Obese patients (BMI>35)
2. Pregnant females.
3. History of cholecystectomy.
4. Patients taking antihypertensive drugs acting on the autonomic nervous system.
5. Patients with history of CVA.
6. Patients with significant cardiovascular co-morbidities.
7. Patients with Thyroid dysfunction.
8. Pre-existing hepatobiliary or gastrointestinal disease

**Method to measure gallbladder volume**

An ultrasonographic evaluation of fasting gallbladder volume was done in all the subjects using a 3-5 MHz convex transducer on Siemens Acuson X300 ultrasound machine . The greatest length (L), greatest transverse width (W), and anteroposterior (H) dimensions were recorded. All the measurements were recorded by a single, experienced observer in both the fasting state and one hour after a fatty meal (40 gm fat content).

Gallbladder volume was calculated using ellipsoid method:

$V = \pi/6$ (L X W X H)

Where,

L = Length of gallbladder

W = Maximum width of gallbladder

H = Maximum height of gallbladder

Gallbladder motility was observed

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 fastingand post meal gallbladder volumes. Post meal volume was taken one hour after giving fatty meal i.e. four slice of bread with 40 gm butter. The percentage of gallbladder contraction was calculated by the formula.

The percentage of gallbladder contraction was calculated by the formula:

Ejection fraction was calculated as:

EF = Vf - Vp x 100 Vf

Where EF= ejection fraction (Vf= fasting gall bladder volume, Vp= post prandial gall bladder volume)

Hence, gall bladder volumes and ejection fractions were compared among diabetics with and without neuropathy and among controls.

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

**Statistical analysis**

The software used for statistical analysis was SPSS (Statistical product and service solution) . The

statistical tests performed was unpaired t-test and paired t-test.

Qualitative variables were compared using proportions and quantitative variables were compared using mean values. Significance level was fixed at P <0.05

## RESULTS

[Table 1] shows gender wise distribution of cases. In the Case group there were 53 (53% Male & 47 (47%) Females whereas in the Control groups Males were 32(64%) and Females were 18 (36%). Average Fasting Blood Glucose among Cases were 142.59+27.14 mg/dl and control were 91.34+9.32 mg/dl and Average Post-Prandial Glucose were 169.05+31.74 mg/dl among Cases and 114.65+10.77 mg/dl among controls. Average HbA1c among Cases were 7.52+1.11and control were 5.17+0.27

FASTINGVF among Cases were13.09+4.39and control were 16.36+3.3 (p<0.001).

GBVOLPPamong Cases 20.62+12.86 andcontrol were12.23+3.92 (p=0.001)

EJECTFRACTamong Cases 20.62+12.86 and control were25.89+12.53.

AUTONEUROPATHY was found in 55% among cases and 0 in control.

Among Cases Autoneuropathy was, Mild in 13%, Moderate in 36% and severe in 51% by Ewing and Clarke criteria. Correlation coefficients of HbA1c with Diabetic Neuropathy and Fasting GB Volume showed moderate positive correlation.

**Table 1: Distribution of Cases according to Gender**

| Sex | Case (n=100) | Control (n=50) |
|---|---|---|
| Male | 53 (53%) | 32 (64%) |
| Female | 47 (47%) | 18 (36%) |

[Table 1] shows gender wise distribution of cases. In the Case group there were 53 (53% Male & 47 (47%) Females whereas in the Control groups Males were 32(64%) and Females were 18 (36%).

**Table 2: Distribution of cases according to Age**

| Age (Yrs) | Case | % age | Mean +SD | Control | % age | Mean +SD |
|---|---|---|---|---|---|---|
| <40 | 21 | 21% | | 3 | 6% | |
| 41-50 | 28 | 28% | 51.80+12.87 | 15 | 30% | 58.34+11.65 |
| 51-60 | 24 | 24% | | 15 | 30% | |
| 61-70 | 22 | 22% | | 8 | 16% | |
| >71 | 5 | 5% | | 9 | 18% | |

[Table 2] shows distribution of cases according to age. In the Case group there were 21 (21%) below 40 years, 28 (28%) were in the 41-50 age group, 24 (24%) in the 51-60 age group, 22 (22%) in the 61-70 age group and 5 (5%) were more than 70 years age. While in the Control group there were 3 (6%) below 40 years, 15 (30%) were in the 41-50 age group, 15 (30%) in the 51-60 age group, 8 (16%) in the 61-70 age group and 9 (18%) were more than 70 years age.

**Table 3: Demographic Data and Investigations.**

| Variables | Case | Control | P Value |
|---|---|---|---|
| Age | 51.80+12.87 | 58.34+11.65 | |
| Sex M/F | (53%)/(47%) | (64%)/(36%) | |
| Height | 166.52+7.53 | 165.80+9.52 | 0.78 |
| Weight | 67.01+14.23 | 65.99+12.54 | 0.89 |
| BMI | 24.14+4.77 | 24.13+4.71 | 0.18 |
| DM YES/NO | (100%)/0 | (0/100%) | |
| SBP | 130.22+17.26 | 129.80+16.27 | 0.86 |
| DBP | 81.60+9.32 | 81.72+9.54 | 0.19 |
| AFBS | 142.59+27.14 | 91.34+9.32 | 0.001 |
| APPBS | 169.05+31.74 | 114.65+10.77 | 0.001 |
| HbA1c | 7.52+1.11 | 5.17+0.27 | 0.001 |
| CRETNINE | 1.05+0.21 | 1.03+0.17 | 0.79 |
| FASTING VF | 13.09+4.39 | 16.36+3.35 | 0.001 |
| GBVOLPP | 20.62+12.86 | 12.23+3.92 | 0.001 |
| Eject Fract | 20.62+12.86 | 25.89+12.53 | 0.001 |
| Autoneuropathy Y/N | 55%/45% | 0%/100% | |
| Mild | 13% | 0 | |
| Moderate | 36% | 0 | |
| severe | 51% | 0 | |

Data are presented as means ± SD or as actual number (n). P values correspond to the differences between the two groups by unpaired t-tests for continuous variables and Chi-square test for medications.

**Table 4: Distribution of cases according to GB Fasting Volume**

| Volume | Mean | SD | P Value |
|---|---|---|---|
| Case | 13.09 | 4.39 | P<0.05 (S) |
| Control | 16.36 | 3.35 | |

**Table 5: Distribution of cases according to GB VOLUME PP**

| Volume | Mean | SD | P Value |
|---|---|---|---|
| Case | 20.62 | 12.86 | P<0.05 (S) |
| Control | 12.23 | 3.92 | |

**Table 6: Distribution of cases according to Ejection Fraction**

| Volume | Mean | SD | P Value |
|---|---|---|---|
| Case | 20.62 | 12.86 | p<0.05 (S) |
| Control | 25.89 | 12.53 | |

**Table 7: Correlation coefficients of HbA1c with Fasting GB Volume**

| | Case | | Control | |
|---|---|---|---|---|
| Variable | r | p value | r | p value |
| HbA1c | 1 | 0.00 | 1 | 0.02 |
| FASTING GB VOL | -0.027 | 0.789 | -.206 | 0.151 |

**Table 8: Correlation coefficients of HbA1c with PP GB Volume**

| | Case | | Control | |
|---|---|---|---|---|
| **Variable** | **r** | **p value** | **r** | **p value** |
| HbA1c | 1 | 0.03 | 1 | 0.02 |
| PP GB VOL | 0.081 | 0.48 | -.192 | 0.181 |

**Table 9: Correlation coefficients of HbA1c with Ejection Fraction**

| | Case | |
|---|---|---|
| **Variable** | **R** | **p value** |
| duration of diabetes | 1 | 0.00 |
| ejection fraction | -0.10 | 0.28 |

## DISCUSSION

Gall bladder abnormalities may be seen in long-standing diabetes, especially those with diabetic neuropathy.[7-10] Diabetes is also a known predisposing factor to emphysematous cholecystitis.[11,12] In this study, the FGBV was significantly higher in diabetic patients with neuropathy than in those without neuropathy [Table 4]. The FGBV with neuropathy was also higher than in the control group, though this was not statistically significant.

Singh et al,[12] found that FGBV in patients with neuropathy was higher than in those without neuropathy, although the difference was statistically insignificant, unlike in our study. Furthermore, in Singh et al study, the FGBV of patients with neuropathy was significantly higher than that of controls; in our study, the difference was statistically insignificant.

The increased FGBV seen in this study is similar to the findings of Sharma et al,[13] who also found that subjects with neuropathy had a significantly larger FGBV. However, our findings are at variance with the findings of Keshavrzzian et al,[14] who reported that gall bladder dysfunction is rare in diabetes. The PPGBV in those with neuropathy was significantly higher than in those without and in controls. This finding is similar to what was observed in the study by Ertugrul et al.[15]

Other studies also established a similar pattern among the three study groups.[18] The GBCI, which is a measure of the ejection fraction, was significantly impaired in patients with neuropathy compared with the controls and those without neuropathy. Similar findings were documented by Singh et al,[12] who reported that GBCI was reduced in diabetic patients compared with a control group; and was further reduced in diabetic patients with neuropathy, although this was not statistically significant.

Guliter et al,[16] and Agarwal et al,[17] also demonstrated gall bladder ejection impairment in diabetic patients with neuropathy. The mean age of those with neuropathy was significantly higher than those without neuropathy in this study. Furthermore, the duration of the disease was significantly longer in diabetes with neuropathy. This is consistent with the findings of Singh et al,[12] who reported that autonomic neuropathy became more prevalent with increasing duration of illness. Therefore, relationships thus exist between the duration of diabetes, FGBV, and GBCI. The mean FGBV was highest in the group that had the highest mean duration of diabetes, i.e. the diabetic group with neuropathy. The prevalence of gallstone in diabetes was 15% in this study. Females had a higher prevalence in all the three groups [Table 2]. Similar findings were reported by Hahn et al.[11]

The exact mechanisms for gall bladder dysfunction in diabetes patients are not known. Pazzi et al,[18] reviewed gall bladder motor function in diabetes and proposed that the mechanism of gall bladder emptying abnormalities may represent a manifestation of denervation caused by visceral neuropathy, a decreased sensitivity of smooth muscle of the gall bladder to plasma cholecystokinin, and/or decreased cholecystokinin receptors in the gall bladder wall. Hahn, et al,[11] suggested that impairment of gall bladder motility complicated by autonomic neuropathy causes stasis and results in cholesterol gall stone crystal formation and gall stone growth. Since gall bladder abnormalities may be asymptomatic in diabetic patients, gall bladder ultrasonography should be considered in the management of diabetic patients, to facilitate proactive management of gall bladder complications and its attendant morbidity/mortality. Ultrasonography is cheap and usually readily available, and does not utiliseionising radiation.

## CONCLUSION

This study concludes that there are high incidence of gall bladder contractile dysfunction in diabetic patients as compared to healthy controls. Further gall bladder dysfunction shows moderate positive correlation with HbA1c levels. Also we conclude that contractile dysfunction is more severe in Diabetics with cardiac autonomic neuropathy.

Therefore it is suggested that diabetic patients with autonomic dysfunction should be carefully evaluated for gall bladder dysfunction by non-invasive method like ultrasonography so as to prevent future complication related to gall bladder like cholecystomegaly, cholelithiasis, cholecystitis etc.

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