

Original Research Article

Gall bladder ejection fraction as a marker of autonomic neuropathy in type 2 diabetes mellitus

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ABSTRACT

Background: Diabetic neuropathy is one of the commonest complications of diabetes mellitus and associated with considerable morbidity and mortality. The influence of diabetes on gall bladder function was not demonstrated in many studies. In this study, the association of fasting gall bladder volume and gall bladder ejection fraction with degree of cardiac autonomic neuropathy was assessed and correlated with duration of diabetes and severity of diabetes..

Methods: The study was conducted in Government Sivagangai Medical College Hospital, Sivagangai, Madurai during a period of January 2018 to September 2018 as a Prospective observational study conducted among 100 patients in study group and 50 healthy subjects in control group. The aim of the study was to find out the incidence of autonomic neuropathy in study group by simple bed side tests, to determine the fasting gall bladder ejection fraction in diabetics, comparison of gall bladder volume in both study and control group, correlation of gall bladder ejection fraction with autonomic neuropathy.

Results: The incidence of CAN is found to be high with longer duration of the disease and the degree is also correlated with duration of the disease. The correlation coefficient of this association is 0.792 which indicates high correlation. The correlation of severity of DM with incidence and degree of CAN was 0.81 which indicates high correlation and also the study showed an increase in the FGBV and a decrease in the GBEF with increase in the severity of cardiac autonomic neuropathy.

Conclusions: In patients with type 2 diabetes mellitus, the gall bladder ejection fraction is significantly related to the duration of diabetes mellitus and degree of hyperglycemia in addition to cardiac autonomic neuropathy(CAN). Similarly, fasting gall bladder volume (FGBV) is significantly increased in type 2 diabetes mellitus patients with cardiac autonomic neuropathy.

Keywords: Autonomic neuropathy, Gall bladder ejection fraction, Gall bladder volume, Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus is commonest endocrine disorder now a days and its prevalence is continuously rising in India due to spread of modern lifestyle and its associated complications are also increasing. Diabetic

autonomic neuropathy (DAN) is a serious and common complication of diabetes which is least recognized and understood complication of diabetes despite its significant negative impact on survival and quality of life in people with diabetes.^{1,2} A subtype of the peripheral polyneuropathies that accompany diabetes, DAN can involve the entire autonomic nervous system (ANS).

ANS vasomotor, visceromotor, and sensory fibers innervate every organ. DAN may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal (GI), genitourinary, sudomotor, or ocular).³

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. Patients with diabetes mellitus have more fasting volumes of GB and these values were correlated with autonomic neuropathy in diabetic patients.

The reason behind this cholecystoparesis is vagal neuropathy. This leads to incomplete emptying of gall bladder that in turn causing cholesterol sequestration and formation of nidus. Postprandial gall bladder emptying has decreased in diabetics those with autonomic neuropathy and has larger residual volume than control. Many studies showed increased prevalence of gall bladder disease in diabetics.⁴⁻⁶

Which is attributed to enlarged gall bladder and impaired gall bladder contraction, mainly due to autonomic neuropathy seen in chronic diabetics. 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.⁷ Cardiovascular Autonomic Neuropathy (CAN) is one of the most overlooked and dreadful complications of Diabetes and it is clinically important because of its life threatening consequences.

The damage to the autonomic nerve fibres innervating the heart and blood vessels results this CAN and it causes abnormalities in control of heart rate and vascular dynamics. Ultrasound is a noninvasive, non-ionizing, relatively cheap and readily available imaging modality. Ultrasonography provides reasonably accurate method of assessing gall bladder volume. The present study is designed to assess the cardiovascular autonomic function in type 2 DM.

In this study, an effort is made to correlate the gall bladder volume and ejection fraction of gall bladder by noninvasive USG method with diabetic autonomic neuropathy especially cardiac autonomic neuropathy. The Aim and Objective of this study was to assess the cardiovascular autonomic function and neuropathic changes in type 2 DM and to correlate the gall bladder volume and ejection fraction of gall bladder by noninvasive USG method

METHODS

This study was conducted among 100 type 2 diabetic patients attending general medicine outpatient department at Government Sivagangai Medical College Hospital, Sivagangai, Madurai with the inclusion criteria, Duration of diabetes >5 years and functioning gall bladder.

The following were the Exclusion criteria:

- Diabetic patients on antihypertensive drugs that interfere with functions of autonomic nervous system
- Overweight subjects (BMI >25)
- Pregnant and lactating females
- With history of major cardiac arrhythmias
- Diabetes mellitus with acute complications
- Angina and MI
- Liver, renal and cardiac failure
- Use of OCPs
- Patients with gall stone disease or hepatobiliary diseases
- Patients with history of abdominal surgeries other than postpartum sterilization
- History of CVA.

Control group

Age and sex matched 50 healthy subjects were selected after getting informed consent. The same exclusion criteria were applied to control group also. Institutional Ethical Committee approval was obtained before starting the study.

Study procedure

History regarding symptoms of autonomic neuropathy and duration of diabetes, clinical examination and routine blood investigations were done. Cardiac autonomic neuropathy was assessed by using simple non-invasive bedside tests. These tests were heart rate variation with deep respiration, immediate heart rate response to standing, blood pressure response to standing and blood pressure response to sustained hand grip. Fasting gall bladder volume was assessed in both study and control group using ultrasonography.

Then the patients were given standardized fatty meal. Then the one hour postprandial gall bladder volume was measured in the same way as fasting gall bladder volume. Then the gall bladder ejection fraction was calculated using the formula, gall bladder ejection fraction=(fasting gall bladder volume-postprandial gall bladder volume)/fasting gall bladder volume, then multiplied by 100.

Statistical analysis

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done

with the help of computer by using SPSS software and Sigma Stat 3.5 version (2012). Using this software, percentage, mean, standard deviation and 'p' value were calculated through one way ANOVA, Pearson correlation and Chi square test and P value of <0.05 was taken as significant.

RESULTS

Age and sex distribution

The study population for type 2 Diabetes mellitus consisted of 100 patients (46 males and 54 females) and the control group consisted of 50 subjects (23 males and 27 females). The cases were in the age group of 40-80 years. Forty five percent of the cases were in the age group of 51-60 years. 18% belonged to age group of 41-50 years. 34% belonged to the age group of 61-70 years. Only 3% belonged to age group of 71-80 years.

Duration of diabetes

All the patients in the study group had duration of the disease for more than 5 years. The cases and control subjects were divided into 3 groups according to the duration of the disease. Forty two percent patients had disease for 5-10 years, 32 patients had for 11-15 years and 26 patients had for more than 15 years.

Cardiac autonomic neuropathy in T2DM and controls

Among the 100 cases of Type 2 Diabetes mellitus, 78 had cardiac autonomic neuropathy. Of these 78 cases, 16 had Grade I cardiac autonomic neuropathy, 28 and 34 Grade II and Grade III cardiac autonomic neuropathy respectively. In the control group, 3 and 2 had Grade I and Grade II cardiac autonomic neuropathy respectively. (Table 1).

Table 1: Cardiac autonomic neuropathy in T2DM and controls.

Grading	Cases			Controls		
	Male	Female	Total	Male	Female	Total
Grade 0	10	12	22	20	25	45
Grade 1	09	07	16	02	01	03
Grade 2	07	21	28	01	01	02
Grade 3	20	14	34	0	0	0

Severity of diabetes based on PPBS

The type 2 diabetes mellitus cases were grouped into three groups based on the values of PPBS and named as mild, moderate and severe hyperglycemia. 23 patients had mild hyperglycemia with PPBS less than 250 mg%, 17 and 60 had moderate and severe hyperglycemia with PPBS 250 to 300mg% and >300 mg% respectively.

Fasting gall bladder volume in cases and control

The fasting gall bladder volume was measured using ultrasonogram and the study and control population were grouped into three groups based on the CAN prevalence. The control group was named as Group A. The type 2

diabetes mellitus cases without CAN were group in Group B and the cases in the study group with CAN were grouped in Group C. The mean fasting gall bladder volume of group A is 19.9 ml, group B is 24.18 ml, group C is 33.55 ml. The fasting gallbladder volume was highest in group C, then in group B when compared to group A (Table 2).

Gall bladder ejection fraction in controls and cases

The gall bladder ejection fraction was calculated and its mean value of group A, B and C were 60.68, 49.33 and 29.3 respectively. The gall bladder ejection fraction was decreased in group C i.e. DM patients with CAN. (Table 2).

Table 2 : Fasting gall bladder volume and ejection fraction in cases and control.

Groups	Name of the group	No. of cases	Mean fasting gall bladder volume (ml)	Mean gall bladder ejection fraction
Control	A	50	19.9	60.68
DM without CAN	B	22	24.18	49.33
DM with CAN (grade 1-3)	C	78	33.55	29

Correlation between duration of diabetes mellitus and cardiac autonomic neuropathy

Among 42 cases of DM with duration of the disease 5- 10 years, 18 patients did not have any CAN features.16 patients had Grade I, 7 patients had Grade II and 1 had Grade III CAN. The patients with disease for 11-15 years were 32 AND among them, 2 did not have CAN and 0, 21 and 9 patients had CAN Grade I, II and III respectively.

Similarly, 26 patients had disease for >15 years. Out of these 26, 25 had CAN Grade III. The incidence of CAN is found to be high with longer duration of the disease and the degree is also correlated with duration of the disease. The correlation coefficient of this association is 0.792 which indicates high correlation.

Correlation between severity of diabetes mellitus and cardiac autonomic neuropathy

Among 23 cases with PPBS of less than 250 mg%, 16 did not have CAN and 7 had CAN Grade I. Out of 17 cases

of DM with PPBS in between 250 to 300 mg%, 9 and 4 had CAN Gr I and II respectively. And 4 did not have any CAN. Of 60 patients with PPBS >300 mg%, 24 had Grade III CAN and 2 did not have CAN.

The correlation of severity of DM with incidence and degree of CAN was assessed. The correlation coefficient was 0.81 which indicates high correlation.

Mean values of PPBS, FGBV and GBEF in study and control group

The study showed an increase in the FGBV and a decrease in the GBEF with increase in the severity of cardiac autonomic neuropathy.

The mean FGBV was high in the patients with type 2 DM when compared to control subjects. Among patients with DM, the mean FGBV was high for those with CAN than cases without CAN.

Similarly, the GBEF was lower in cases than in controls. And among cases it was much lower in patients with evidence of CAN than patients without CAN.

Table 3: Mean values of PPBS, FGBV and GBEF among diabetics and normal individuals.

Grades	Cases			Controls		
	PPBS	FGBV	GBEF	PPBS	FGBV	GBEF
Grade 0	226.3	24.18	49.33	133.31	20	61.69
Grade 1	247.06	25.63	40.73	138	18	51.86
Grade 2	312.25	32.96	31.96	140	20.5	51.08
Grade 3	322.94	37.76	21.73	0	0	0

DISCUSSION

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of DAN has not been fully appreciated. Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. Whereas symptoms suggestive of autonomic dysfunction may be common they may frequently be due to other causes rather than to true autonomic neuropathy. Subclinical autonomic dysfunction can, however, occur within a year of diagnosis in type 2 diabetes patients and within two years in type 1 diabetes patients.⁸ Because of its association with a variety of adverse outcomes including cardiovascular deaths, cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of DAN. The introduction over 20 years ago of simple, noninvasive

tests of cardiovascular autonomic function has supported extensive clinical and epidemiologic investigation of CAN. The data forms the strongest body of evidence for the importance of detecting and monitoring impaired autonomic function in patients with diabetes.^{9,10} Neural control of gallbladder emptying is mediated by both parasympathetic and sympathetic innervation; the former increases gallbladder contractility and the latter causes relaxation. Meal-related release of CCK causes gallbladder contraction. The motility defects of gallstone patients are manifested by increased fasting volume, decreased ejection fraction, decreased rate of ejection, and increased residual volume of the gall bladder. Our study has shown that among the 100 cases of Type 2 Diabetes mellitus, 78 had cardiac autonomic neuropathy. Of these 78 cases, 16 had Grade I cardiac autonomic neuropathy, 28 and 34 Grade II and Grade III cardiac autonomic neuropathy respectively. Similarly a study done by Lina Alolaiwi et al,¹¹ presented that the CAN was present in 15.6%: 2.9% with OH, 5.8% with RT and

8.4% with prolonged QTc. Prolonged T2D duration and anti-HTN were independently associated with CAN. It has been proved in many studies that the duration of diabetes and poor glycemic control are the important risk factors for the development of CAN. In our study the mean fasting gall bladder volume of control group was 19.9 ml, Diabetics without CAN was 24.18 ml, Diabetics with CAN was 33.55 ml.

The fasting gallbladder volume was highest in Diabetics with CAN, then in Diabetics without CAN when compared to controls. Gall bladder ejection fraction was found to be very less among diabetics with autonomic neuropathy. The findings were similar to many other studies which showed that gallbladder emptying (both its rate and extent) as a measure of gallbladder motility and found that the gallbladder emptying rate and/or the gallbladder emptying were also reduced in diabetics.¹²⁻¹⁵

In our study it is evident that an increase in the FGBV and a decrease in the GBEF with increase in the severity of cardiac autonomic neuropathy. The mean FGBV was high in the patients with type 2 DM when compared to control subjects.

Among patients with DM, the mean FGBV was high for those with CAN than cases without CAN. Similarly, the GBEF was lower in cases than in controls. And among cases it was much lower in patients with evidence of CAN than patients without CAN. Further studies showed that Patients of diabetes mellitus had statistically significant larger fasting gall bladder volumes and these values were highly significant amongst patients with autonomic neuropathy, Patients of diabetes mellitus and statistically significant larger post fatty meal gall bladder volume and these values were highly significant in patients with autonomic neuropathy.¹⁶ Diabetics with longer duration of disease had poorer gall bladder contractility ($p < 0.05$). Nevertheless, all diabetics can be evaluated for the presence of increased fasting gallbladder volumes, impaired postprandial gallbladder emptying, and gallbladder sludging as screening process with ultrasonography.

CONCLUSION

In our study it is evident that the duration of diabetes was the important predictor of cardiac autonomic neuropathy and the neuropathic changes in diabetics has influenced the gall bladder function in terms of high gall bladder volume and the low gall bladder ejection fraction because of altered gall bladder motility due to the severity and the higher the grade of autonomic neuropathy compared to healthy control population. We therefore conclude that impaired gall bladder contraction was found amongst patients of diabetes mellitus with autonomic neuropathy.

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Conflict of interest: None declared

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

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