



## Original Research Article

# Gall bladder dysfunction in correlation with autonomic neuropathy in type 2 diabetes

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## ABSTRACT

**Introduction:** Diabetic Autonomic Neuropathy (DAN) is one of the complications of diabetes mellitus causing impaired autonomic control over cardiovascular, gastrointestinal systems. There is increased incidence of gallbladder diseases in diabetic patients attributed to gallbladder dysfunction caused by autonomic neuropathy. This study is undertaken to support the evidence of gall bladder dysfunction can be considered as indicator of autonomic neuropathy in type 2 diabetes mellitus.

**Aim:** To study the gall bladder ejection fraction in Type 2 diabetics and comparison of gall bladder ejection fraction in diabetics with healthy control group.

**Materials and Methods:** 100 Type 2 diabetics and 20 healthy controls were taken for study. Subjects cardiac autonomic tests and laboratory investigations were done. Gallbladder volumes (fasting and postprandial) and ejection fraction were considered.

**Results:** Mean gall bladder volumes (fasting and post prandial) was higher in subjects with Type 2 diabetes compared to control group. Mean gall bladder ejection fraction was lower in subjects with diabetes as compared to controls difference was not significant ( $p < 0.45$ ).

Mean gall bladder volumes (fasting and post prandial) was increased in Type 2 diabetics with CAN compared to Type 2 diabetics without CAN. Mean gall bladder ejection fraction was decreased in Type 2 diabetics with CAN compared to Type 2 diabetics without CAN difference was statistically significant ( $p < 0.00037$ ).

**Conclusion:** Thus from the study can conclude that gallbladder dysfunction involving gastrointestinal system can be taken as indicator of autonomic neuropathy in diabetes.

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## 1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by increased glucose levels resulting from defects in insulin production and insulin action or both.<sup>1</sup> India represents 49 percent of the world's diabetes cases, with an estimated 72 million cases in 2017.<sup>2</sup> Diabetic Autonomic Neuropathy (DAN) is one among the complications of DM causing impaired autonomic control over cardiovascular, gastrointestinal, and genitourinary

systems. Diabetic Cardiac Autonomic Neuropathy (CAN) is the most recognized component of DAN, which has positive correlation with increased morbidity and mortality.<sup>3</sup> Gall bladder is one among affected organs in chronic diabetics.<sup>4</sup>

Few previous studies have shown increased prevalence of gall bladder dysfunctions and its complications in diabetic patients, attributed to cholecystomegaly and impaired motility of gall bladder manifested by high fasting volume, less ejection fraction, low rate of ejection, and high residual volume of the gall bladder, which are mainly due to autonomic neuropathy commonly seen in chronic diabetics.<sup>5,6</sup>

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This study is intended to support that ultrasonic evidence of gall bladder dysfunction can be considered as indicator of autonomic neuropathy in type 2 diabetic patients.

## 2. Aims and Objectives

1. To determine gall bladder ejection fraction in type 2 diabetes patients.
2. Comparison of gall bladder ejection fraction in diabetic group with healthy control group.
3. Comparison of gall bladder ejection fraction in diabetics with and without autonomic neuropathy.

## 3. Materials and methods

The study was conducted in Krishna Rajendra Hospital attached to Mysore Medical College and Research Institute from 1st January 2017 to 30th June 2018 (18 Months). The study protocol was approved by the ethical and scientific committees of the institute. 100 type diabetic patients as cases and 20 age and sex matched healthy controls were selected after satisfying inclusion and exclusion criteria. Informed consent was taken from both the groups before enrolment.

### 3.1. Selection of cases group

#### 3.1.1. Inclusion criteria

1. Type 2 DM patients between 18-65years

#### 3.1.2. Exclusion criteria

1. Subjects diagnosed with Type 1 DM.
2. Subjects with the Age <18 years and > 65 years
3. Subjects diagnosed to be having primary hepatobiliary disease.
4. Subjects who have underwent cholecystectomy.

Control group consist of age and sex matched 20 healthy volunteers were recruited to control group after taking informed consent.

#### 3.1.3. Demographic data

1. Clinical History, Examination.
2. Blood investigations: FBS, PPBS, HbA1C

#### 3.1.4. Ultrasonography

An ultra-sonographic evaluation gallbladder volume was done in all subjects. Gallbladder volumes were measured in fasting and 2 hours post-prandial. Gallbladder ejection fraction was calculated using formula.

#### 3.1.5. Cardiac autonomic function tests

Cardiac autonomic neuropathy in diabetic patients was assessed clinically by using simple non-invasive cardiovascular bedside tests, which included

1. Resting Heart Rate: >100 beats/min is abnormal.
2. Heart rate response to deep breathing (E: I ratio).
3. Heart rate response to standing.
4. Postural hypotension.

#### 3.1.6. Statistical methods

Descriptive statistical analysis has been conducted in present study. Results on continuous measurements are presented on Mean + SD and results on categorical measurements are presented in Number (%). Significance is considered at 5 % level of significance. Student t test is done to identify significance of study parameters on continuous scale between two groups on metric parameters, Chi-square/ Fisher Exact test have been used to identify the significance of study parameters \

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for analysis of data and Microsoft word and Excel have been used to generate graphs, tables.

## 4. Results

In these study many of subjects with type 2 diabetes and controls were between 46 – 55 years. As shown in Table 1 in these study 45% of subjects with type 2 diabetes had cardiac autonomic neuropathy as compared to 20% of controls, difference was statistically significant ( $p < 0.038$ ).

As shown in Table 2, the mean fasting gall bladder volume was increased in subjects with type 2 diabetes (13.82 + 4.31 ml) compared to controls (12.39 + 3.63 ml). The mean postprandial gall bladder volume was increased in subjects with type 2 diabetes (7.84 + 3.60 ml) as compared to controls (6.62 + 2.12 ml). The mean gall bladder ejection fraction was less in subjects with type 2 diabetes (44.64 + 11.45%) as compared to controls (46.40 + 8.78%) in the present study difference was not statistically significant ( $p < 0.45$ ). {Figure 1}

As shown Table 3, the mean fasting gall bladder volume was increased in type 2 diabetics with CAN (14.88 + 4.28 ml) compared to type 2 diabetics without CAN (12.96 + 4.09 ml). The mean postprandial gall bladder volume was increased in type 2 diabetics with CAN (9.21 + 4.23 ml) compared to type 2 diabetics without CAN (6.71 + 2.43 ml). The mean gall bladder ejection fraction was lower in type 2 diabetics with CAN (40.2 + 13.75%) compared to type 2 diabetics without CAN (48.2 + 7.24%) in the present study the difference was statistically significant

( $p < 0.00037$ ). {Figure 2} This shows that subjects with type 2 diabetes with CAN had higher mean fasting and postprandial gallbladder volumes and lower mean gallbladder ejection fraction showing autonomic neuropathy of gallbladder in the present study.

**Table 1:** Cardiac autonomic neuropathy among subjects with type2 diabetes and controls.

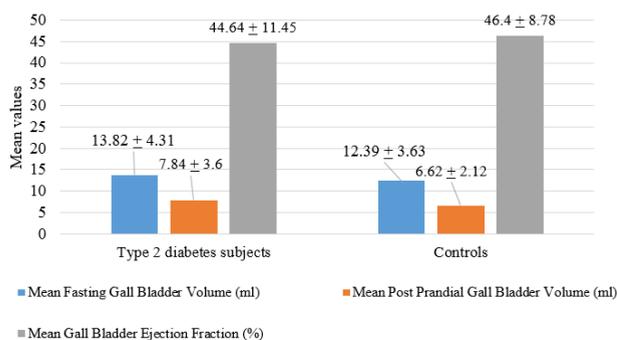
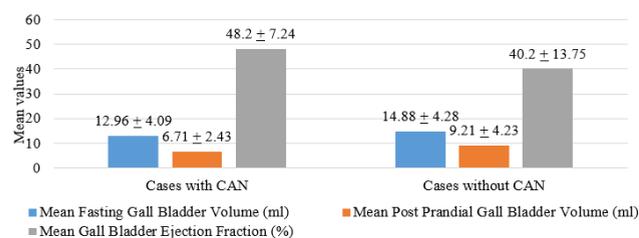
CAN	Type 2 diabetics (n=100)	Controls (n=20)
Present	45 (45%)	4 (20%)
Absent	55 (55%)	16 (80%)

**Table 2:** Mean gallbladder volumes and mean ejection fraction among subjects with type 2 diabetes and controls in the present study.

	Mean fasting gallbladder volume + SD (ml)	Mean postprandial gallbladder volume + SD (ml)	Mean gallbladder ejection fraction + SD (%)
Type 2 diabetes subjects (n=100)	13.82 + 4.31	7.84 + 3.60	44.64 + 11.45
Controls (n=20)	12.39 + 3.63	6.62 + 2.12	46.40 + 8.78

**Table 3:** Mean gallbladder volumes and mean ejection fraction among subjects with type 2 diabetes with CAN and without CAN

	Mean fasting gallbladder volume + SD (ml)	Mean postprandial gallbladder volume + SD (ml)	Mean gallbladder ejection fraction + SD (%)
Type 2 diabetics without CAN (n=45)	12.96 + 4.09	6.71 + 2.43	48.2 + 7.24
Type 2 diabetics with CAN (n=55)	14.88 + 4.28	9.21 + 4.23	40.2 + 13.75

**Fig. 1:** Mean gallbladder volumes and mean ejection fraction among subjects with type 2 diabetes and controls**Fig. 2:** Gallbladder volumes and ejection fraction among type 2 diabetes subjects with CAN and without CAN

## 5. Discussion

In present study mean gall bladder volume was increased in subjects with type 2 diabetes compared to controls. This is in accordance with study of AK Aggarwal et al,<sup>7</sup> JS Hahm et al,<sup>8</sup> MP Sharma et al,<sup>9</sup> AM Bucceri et al.<sup>10</sup>

In present study the mean fasting gall bladder volume was increased in type 2 diabetics with CAN compared to without CAN. This is in accordance with study of Kalyani DV et al.<sup>4</sup>

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. 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.<sup>4</sup> The high prevalence of gall stone disease in diabetics include; less gall bladder motility, less postprandial cholecystokinin (CCK) release, less sensitivity of gall bladder smooth muscle to CCK, less number of CCK receptors in the gallbladder wall and supersaturation of bile. Neural control of gallbladder emptying is controlled by both parasympathetic and sympathetic innervation.<sup>7</sup> The reason behind 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 diabetic patients with autonomic neuropathy and has larger residual volume than control. Many studies have high prevalence of gall bladder dysfunction in diabetics. Which will lead to increased size of gall bladder and disarranged gall bladder contraction, mainly due to autonomic neuropathy seen in chronic diabetics. Increased fasting gall bladder volume and low percentage of contraction both are observed

in patients of chronic diabetes mellitus attributed to autonomic neuropathy. For long time stasis of bile leads to complications e.g. cholelithiasis, cholecystitis and sludge deposition as late outcome.<sup>4</sup>

## 6. Conclusion

In the present study there is high gall bladder volume and low ejection fraction which may be due to neuropathy changes in diabetes leading to decreased gall bladder motility which conclude that gall bladder ejection fraction can be used as a marker of autonomic neuropathy in Type 2 Diabetes Mellitus.

## 7. Acknowledgment

None.

## 8. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

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