ULTRASONOGRAPHIC EVALUATION OF THE GALLBLADDER IN TYPE II DIABETES MELLITUS PATIENT IN OBAFEMI AWOLOWO UNIVERSITY TEACHING HOSPITAL COMPLEX; ILE-IFE

BY

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A DISSERTATION SUBMITTED TO THE FACULTY OF RADIology, NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PART FULFILMENT OF THE AWARD OF THE FELLOWSHIP OF THE COLLEGE IN RADIology (FMCR)

NOVEMBER, 2012
ATTESTATION

We certify that the dissertation titled “Ultrasonographic evaluation of the gallbladder in type II diabetes mellitus in ile-ife” has been reviewed by us and we supervised the conduct of the study.

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Certification

We certify that this dissertation titled “Ultrasound Evaluation of the Gallbladder in type II Diabetes mellitus patients in ile-ife” has been reviewed by us and we supervised the conduct of the study.

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DEDICATION

This book is dedicated to God almighty for seeing me through this struggle, my family for the wonderful support, and my teachers for wealth of experience shared.
ACKNOWLEDGEMENT

My gratitude goes to the Almighty God who has made this work a possibility despite all odds.

Special thanks go to my two wonderful supervisors, Professor V.A. Adetiloye and Dr O.O Ayoola.

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I am most grateful to God for the support from my wonderful family.
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SUMMARY

INTRODUCTION / BACKGROUND

Ultrasonography is an important tool in assessing gallbladder function and disorder in diabetics, bearing in mind neuropathy which is one of the long time complications, especially in type II diabetes mellitus (DM), which may affect gall bladder tone and emptying. This study evaluated gallbladder (GB) changes (fasting and postprandial) in type II DM using ultrasonography.

AIMS AND OBJECTIVES

Evaluating gallbladder volume and contractility index in this patients, as well as determining if there is any correlation with duration of DM and associated gall bladder stone.

METHODS

A prospective sonographic evaluation of the gall bladder in fasted and 45min postprandial 100 type II DM subjects ( 50 subjects with neuropathy and 50 without neuropathy ), as well as control normal healthy individuals was carried out in the Radiology department of Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile-Ife.

DATA ANALYSIS

Data obtained from this study was analyzed using the SPSS (version 16.0) The continuous variables were expressed as mean ± standard deviation and student t-test was used for comparison between the subject groups to determine if there was statistical significance (p<0.05).
RESULTS

Diabetic patients with neuropathy had the highest mean gallbladder volume compare to those without neuropathy and control group. The mean postprandial gall bladder volume was also highest in diabetics with neuropathy. The gallbladder ejection fraction was lowest in diabetics with neuropathy compare to those without neuropathy and control group. Longer duration of illness and doubled prevalence of gall stone is noted in diabetics with neuropathy compare to those without neuropathy and control group.

CONCLUSION

This study revealed that significant number of patients with type II DM has gall bladder abnormalities ranging from increase gall bladder volume to reduced ejection fraction (GBCI) with associated increase prevalence of gall stone disease. This is seen to be worse off in diabetics with neuropathy. Association also was established between duration of diabetes and gall bladder abnormalities.

RECOMMENDATION

Ultrasonography of the gall bladder therefore is highly recommended in type II DM patient management especially in those with long duration of illness as this will aid proactive management of gall bladder complication which they are prone to, and reduce morbidity and mortality.
INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The prevalence of diabetes mellitus is rising worldwide in both developed and developing countries.\(^1\) It’s worldwide prevalence is about 2\%, and the prevalence in Nigeria is 2.2\%, which means that about 2.6 million Nigerians are diabetics.\(^2\) It is known that 50\% of the affected individuals (i.e., about 1.3 million Nigerian diabetics) are unaware that they have the disease.\(^3,4\) Complications of diabetes mellitus have been found to set in long before clinical manifestation of the disease.\(^3,4\) The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart, gall bladder, and blood vessels. Digestive system dysfunction is also an important contributor to morbidity of this disease.\(^5\)

Neuropathy, one of the long term complications of DM which may be autonomic or peripheral, may involve the gastrointestinal tract (GIT) and present with protein manifestation.\(^6,7\) Vagal parasympathetic fibers maintain gall bladder (GB) tone and influence its emptying,\(^8-10\) hence, it’s dysfunction may occur with neuropathy. Abnormalities in gall bladder size and emptying have been reported.\(^10-11\) Diabetes subjects are reported to have a two to three fold increase in the prevalence of cholesterol gallstone, inadequate emptying of gall bladder and increased gall bladder volume has been reported in various studies.\(^11\) But contradictory results also, have been reported by some workers who observe no change in gall bladder emptying in diabetic patients as compared to non-diabetics.\(^15\)
Hypomotility of gallbladder cause gallstone formation in DM and other chronic disorder like obesity, sclerosis and pregnancy.  

In this present study effort was made to evaluate the gallbladder changes in type II DM patients using real time ultrasonography which is an inexpensive, simple and reliable method of evaluating gall bladder function.  

16-19
AIMS AND OBJECTIVES

BROADLY

1. To evaluate gallbladder changes in patients with type II diabetes mellitus

SPECIFICALLY

i. To determine the gallbladder volume (fasting & postprandial), and contractility index (ejection fraction) in patients with type II DM.

ii. To determine the association between gall bladder volume, contractility index and duration of type II DM.

iii. To evaluate associated gallstone prevalence in these patient.
JUSTIFICATION

Diabetic neuropathy one of the complication of type II diabetic patients causes loss of gallbladder tone which predisposes to increased gallbladder volume, stasis, and gallstone formation. Routine screening of this patient’s gallbladder using ultrasonography which is cheap, readily available and non-ionizing will help in the early detection of gallbladder disorder in these patients and aids proactive management of this condition, thus reducing morbidity and mortality. Furthermore, few studies have been reported in this environment on the effect of diabetic neuropathy on gallbladder of type II DM patients. Such as that done by Bohewo and Olokoba in Ilorin.
GROSS ANATOMY OF GALL BLADDER

The gall bladder is a pear-shaped sac attached to the extra hepatic bile ducts by the cystic duct. It is very variable in size but normally measures up to 10 cm in length and 3 cm in diameter. It is described as having a fundus, body and it hangs on its bed on the visceral surface of the liver with its neck lying superiorly and its fundus inferiorly. The gall bladder is covered by peritoneum on its fundus and inferior surface. It may have a mesentery and hanging free from the inferior surface of the liver. The mucosa lining the gall bladder is smooth except at the neck and the cystic duct, where it forms folds that are arranged spirally and called the valves of Hiester.

Anterosuperiorly, it is related to the gall bladder bed of the liver; the fundus is related to the anterior abdominal wall at the point where the lateral edge of the right rectus muscle meets the ninth costal cartilage; and posteroinferiorly the neck is related to the lesser omentum, the body to first part of the duodenum and fundus to transverse colon. Normal variations include septum within the lumen; fundus may be folded back on itself (Phrygian cap); diverticula’s may occur anywhere, its location may be retro hepatic or suprahepatic and location may be intrahepatic (normal in the fetus up to 2 months). Others include left sided location, absent gall bladder (very rare) and double gall bladder.

The gall bladder is supplied by the cystic artery, a branch of the right hepatic artery and by branches that supply it directly from the liver in the gall bladder bed. Blood from the gall bladder drains through small veins to the liver, from the gall bladder bed. Sometimes a cystic vein is formed that drains to the portal veins.
**Fig.1:** Schematic sketch of the gallbladder.
SONOGRAPHIC ANATOMY OF GALL BLADDER

The gall bladder can be visualized between the liver and the right kidney (see fig.2). Its wall thickness varies with the degree of distension. The size of the gall bladder varies also between the fed and fasting states, but can be up to 10cm long and 3cm wide. The position of the fundus can be as low as the pelvis. The normal wall is seen as a thin echogenic wall less than 3mm thick and it contains clear sonolucent bile.\(^{20}\)

The spiral valves of Heister in the gall bladder neck and cystic duct may cast acoustic shadows that must not be confused with calculi. The hepatic and common bile ducts can sometimes be visualized throughout their course, but part of the common bile duct is often obscured by gas as it passes posterior to the first part of the duodenum.\(^{20}\)
Fig. 2: Longitudinal sonographic appearance of a normal gallbladder.
BRIEF PHYSIOLOGY

As food begins to be digested in the upper gastrointestinal tract, the gallbladder (GB) begins to empty, especially when fatty foods reach the duodenum about 30 minutes after a meal. The mechanism of GB emptying is rhythmical contractions of the wall of the GB, but effective emptying also requires simultaneous relaxation of the sphincter of Oddi, which guards the exit of the common bile duct into the duodenum. The most potent stimulus for causing the GB contractions is the hormone cholecystokinin.

The stimulus for cholecystokinin entry into the blood from the duodenal mucosa is mainly the presence of fatty foods in the duodenum. In addition to cholecystokinin, the GB is stimulated less strongly by acetylcholine-secreting nerve fibres from both vagi and the intestinal enteric nervous system. They are same nerves that promote motility and secretion in other parts of the upper GIT.
LITERATURE REVIEW

Diabetic autonomic neuropathy gives rise to varied manifestations in the gastrointestinal tract i.e. gastropathies, nocturnal diarrhea, esophageal dysmotility, constipation and gall bladder dysfunction, being consequence of vagal neuropathy leading to reduced gastrointestinal motility. Gall bladder involvement in diabetic autonomic neuropathy is in form of high incidence of gall bladder stones and a significant increase in gall bladder volume with poor concentration and lack of symptoms of gall bladder disease.\textsuperscript{21}

Sigh et al\textsuperscript{21} studied the prevalence of gall bladder disorder on type II DM, correlating gall bladder disease with duration of DM and also comparing gall bladder diseases in patients with or without autonomic neuropathy (AN) as well as normal individuals. His finding reveals that Autonomic neuropathy (AN) becomes more prevalent with increasing duration of diabetes.

Other findings include, significant higher prevalence of gall bladder disease in diabetics with AN as compared to controls but no significant difference in the prevalence of gall bladder disease among diabetics with and without neuropathy. Fasting gall bladder volume of diabetes with AN was significantly higher than that of controls. Fasting gall bladder volume of diabetics with AN was higher than those without AN, although not statistically significant (P>0.10). The percentage of gall bladder contraction is reduced in diabetics as compared to controls and is further reduced in diabetics with AN though not statistically significant.\textsuperscript{21}

Sharma et al studied 52 diabetic patients and fifteen healthy control subjects prospectively for their gall bladder function by ultrasound examination\textsuperscript{22}. Diabetics with
longer duration of disease had poorer gall bladder contractility (P<0.05). Patients with AN had significantly larger fasting gall bladder volume (FGBV) but normal contractility. This result suggests that long standing diabetes may have poor gall bladder empty predisposing to gall stone formation and that patients with AN have reduced tone of fasting gall bladder but normal contractility.\textsuperscript{22}

Keshavrrzzian et al,\textsuperscript{15} evaluated gall bladder function in 27 healthy male volunteers and 47 insulin requiring male diabetics, from an outpatient clinic. The data acquired suggested that gall bladder dysfunction in diabetic males requiring insulin is rare. Haffner SM et al,\textsuperscript{23} examined 462 diabetic individuals. In this study the prevalence of self-reported gall bladder disease was 34.2\% in diabetic women and 7.2\% in diabetic men. Although duration of diabetes was positively related to the prevalence of gall bladder disease (P<0.01), type of therapy was not associated, and fasting glucose concentration was inversely associated with gall bladder disease.\textsuperscript{23}

Haffner SM et al,\textsuperscript{24} examined association between non-insulin dependent diabetes mellitus (NMNM) and the prevalence of gall bladder disease. The authors concluded that women with diabetes have an increased prevalence of gall bladder disease relative to non-diabetic women and that this association is not explained by the greater adiposity or unfavorable body fat distribution of the diabetic subjects.\textsuperscript{24}

Guliter S, et al\textsuperscript{25} evaluated gall bladder volume and motility in non-insulin dependent diabetes mellitus patients using real time ultrasonography, this study was based on the fact that prevalence of cholelithiasis is 2 to 3 times higher in patients with DM than in normal population, especially in NIDDM. The authors investigated the pathogenesis of this increased prevalence by ultrasonography with a brief comparison of
demographic features. This study revealed an increased fasting gall bladder volume and impaired ejection function in NIDDM patients which may be the initiator of bile stasis in the gall bladder and subsequent cholesterol crystal and stone formation.

Agarwal et al., evaluated gall bladder volume in diabetics ultrasonographically, comparing with a control group and correlating gall bladder volume in diabetics with parameters such as age, sex, body mass index, parity, hyperlipidaemia and autonomic neuropathy. Ninety one cases of diabetes mellitus and 40 healthy controls were recruited for the study. Gall bladder volume was found to be significantly positively correlated with age, body mass index, and severity of autonomic neuropathy. In male type II diabetics, gall bladder volume was significantly correlated with waist-hip ratio, gall bladder volume also had significant correlation with proliferative diabetic retinopathy, but not with glycaemic control, microalbuminuria, hypertension, or with duration of diabetes.

Olokoba AB, et al., determine the effect of type 2 DM on fasting gall bladder volume using real time ultrasonography. One hundred type II DM patients and 100 age and sex matched controls underwent real time ultrasonography to determine the effect of type 2 DM on fasting gall bladder volume. The mean gall bladder volume of diabetic patients was $27.6 \pm 15.4\text{ml}$ compared with $24.3 \pm 12.8\text{ml}$ for non-diabetic controls ($P = 0.189$). The authors concluded that type 2 DM is a likely risk factor for increased fasting gall bladder volume in Nigerians.

Olokoba et al., also investigated the risk factors predisposing to gall stone disease amongst patients with type II DM in the same study population. The age, sex, body mass index (BMI), duration of DM and serum lipids were correlated to the
prevalence of gall stone disease in the diabetic patients. The authors concluded that; there was a steady increase in the incidence of gall stone disease with age, the average age of diabetic patients with gall stone disease (GSD) was significantly higher than in those without GSD, the incidence of GSD was commoner in females; the diabetic patient with GSD has higher means value of BMI compared with those without GSD, the mean duration of disease i.e. DM, was higher in those with GS than in those without GS, the mean serum lipids were higher in the diabetic patients with GSD than in those without GSD; and summarily, increasing age is a risk factor for GSD in diabetic patients. Hyperlipidaemia, heavier weight and a longer duration of DM would appear to be associated risk factor.

Same authors also evaluates the relationship between gall stone disease (GSD) and gall bladder (GB) volume using ultrasound in same population, and concluded that gall bladder volume (fasting) tended to be larger in patients with GSD (i.e. in diabetic patients and controls).

These authors further determined the influence of presence of gall stone disease (GSD) in gall bladder wall thickness in the same population and concluded that the presence of GSD appears to increase the thickness of the gall bladder wall (i.e. in diabetic patients and controls).

Olokoba et al., furthermore, studied the prevalence of GSD amongst Nigerians with type II DM in the same study population; they concluded that GSD in Nigerians with type II DM is not a rare occurrence and recommended that right upper quadrant ultrasound scan be advised as part of the routine evaluation of patients with DM.
Rupali et al\textsuperscript{28} reports the prevalence of gallbladder disorder in type 2 diabetics patients and their correlation with sex, age, weight and duration of diabetes. Thirty type 2 diabetes patients and 20 healthy controls underwent real time ultrasonography. Gallbladder disorders such as gallstones, loss of gall bladder tone manifesting as increase fasting volume and reduce gallbladder contraction was noted in type 2 diabetes patients. Mean duration of diabetes was longer in diabetes patient with gallbladder disorder. No significant effect of age, sex, and weight was observed. It was concluded that type 2 diabetic patients have increase prevalence of gallbladder disorder.\textsuperscript{28}

Soad et al,\textsuperscript{29} investigated fasting gallbladder volume and gallbladder emptying in response to a fatty meal in 20 patients with asymptomatic gallstones and compare the results with findings from healthy controls. Compared with control subjects without gallstones, the majority of patients with gallstones exhibited a higher resting gallbladder volume, less fractional emptying after a fatty meal, and a higher post meal residual volume.

Chapman et al,\textsuperscript{13} investigates whether diabetics have increased gallbladder volume that would predispose to stasis, nucleation of cholesterol crystals and gallstone formation by studying 271 diabetic subject and 277 controls with ultrasonography. It was found that gallbladder volume was influenced by both diabetic types. Male had significant larger gallbladder volumes than females.\textsuperscript{31}

Hahn JS et al\textsuperscript{32} compared the gallbladder volume and ejection fraction of 24 diabetics with those of 19 aged –matched and weight-matched controls using real time ultrasonography. This reviewed that gallbladder volume in diabetics was significantly greater compared to that of the control. Moreover in diabetics with autonomic
neuropathy, gallbladder motility was markedly reduced in comparison to diabetics without neuropathy.\textsuperscript{32}

Chapman BA et al, \textsuperscript{33} studied prevalence of gall stone disease in 308 diabetics and 318 controls. Data obtained after statistical analysis reveals that there was higher prevalence of gall stone disease in diabetics compare to controls and that gall stone disease is multifactorial and only in type II DM females was diabetics an independent risk factor.\textsuperscript{33} This further reiterates that gall stone disease is commoner in diabetic patients especially females and it’s prevalence is expected to be even higher in those with neuropathy which is one of the aims and objectives of this study.
MATERIALS AND METHODS

The study was a prospective one that was carried out at the Radiology department of the OAUTHC, Ile-Ife, Osun State between March 2010 to Jan 2011. Approval for the study was obtained from the ethical and research committee of OAUTHC, while an informed consent was obtained from the subjects.

SAMPLE SIZE

Subjects were selected consecutively from out-patient (Endocrinology) clinics and in-patient services (Medical and Surgical wards) at Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife (OAUTHC). For the diagnosis and classification of diabetes, an America Diabetics Association (ADA) criterion of fasting glucose > 126mg/dl was used\textsuperscript{30}. Duration of diabetes was calculated from the time of diagnosis. Demographic data was noted and patients were divided into 2 groups.

- Patients without evidence of neuropathy
- Patients with evidence of neuropathy,

Autonomic neuropathy was considered to be present when patients have at least two abnormal cardiovascular reflexes e.g. impaired heart rate response to vasalva manoeuver, standing or on deep inspiration, and a postural fall on systolic blood pressure of 30mm mercury\textsuperscript{18}. Peripheral neuropathy was diagnosed by impairment in fine touch, pinprick, vibration and position sense and deep tendon reflexes.

The sample size used in this study was calculated using this formula.

\[
N = \frac{Z^2 PQ}{D^2}
\]
Where \( N \) = Sample size

\( Z = \) Standard normal deviation = 1.96

Corresponding to 95% confidence interval

\( P = \) Prevalence of DM in Nigeria is 2.2%.

\( Q = 1 - P \)

\( D = \) Degree of accuracy = 0.05

\[
N = \frac{(1.96)^2 \times 0.02^2 \times 0.978}{(0.05)^2} = 33.
\]

Allowing for better statistical analysis the present study includes 100 diabetic (type II) subjects, out of which 50 were patient’s with neuropathy and 50 without neuropathy. Fifty healthy, non-diabetics, matches for age and sex without symptoms of gallbladder disease make up the control.

**EXCLUSION CRITERIA**

- Subjects with type I DM
- Subjects with liver or biliary disease

**INCLUSION CRITERIA**

- Subjects with confirmed type II DM, with or without clinical evidence of neuropathy.

**EQUIPMENT AND MATERIALS**

These includes

- A Mindray 600 ultrasonic machine with 3.5-5.0 MHZ probe
- Ultrasonic acoustic gel and tissue paper
- Examination couch
PROCEDURE

In the endocrinology clinic and wards patients recruited for this study, with the assistance of the endocrinologist were screened for neuropathy. Information for those that have clinical evidence of neuropathy, biomedical data as well as time of diagnosis was obtained from patient’s case note. Autonomic neuropathy was tested for by taking patient’s pulse rate at rest and a repeat pulse taken when patient has taken deep inspiration and increase his/her intra-abdominal pressure (valsaver maneuver). Patient then breaths normally and after a period of about 5-10 min the pulse rate is taken once again. The pulse rate is expected to normalize after this period to its resting state, impairment of the pulse rate implies autonomic neuropathy. A postural fall in the systolic blood pressure of 30mm Hg when patient changes from supine to recumbent position also indicates autonomic neuropathy. Peripheral neuropathy was diagnosed by impairment in fine touch, pin prick, vibration and position sense and deep tendon reflexes.

In the radiology department real time gray scale ultrasonography was performed using mindray 600 ultrasound machine, with a 3.5 to 5.0 MHZ probe. Scanning was performed after an overnight fast and repeated 45 minutes after ingestion of fatty meal (bread and butter about 40-50g). The skin of the right upper quadrant was covered with ultrasound gel and the probe applied to it. The appropriate depth of focus, frame rate and gain setting were adjusted to obtain an optimal image. Patient was first scanned in the supine position, longitudinally with the probe beveled cephalad. This demonstrates the maximal gallbladder longitudinal outline as well as the anteroposterior dimension (height), fig. 3 & 4.
In the left lateral decubitus position (oblique) the maximum demonstrated transverse dimension (width) was obtained and measured (fig.5) by turning the probe transversely at $90^\circ$ to the longitudinal plane.

Each measurement was taken thrice and the average obtained. Measurement was taken by a single person to reduce intra observer error.
Fig 3: Longitudinal sonogram showing the measurement of the length of gallbladder A-B.
Fig 4: Longitudinal sonogram showing the measurement of the Anteroposterior dimension C-D.
Fig 5: Transverse sonogram showing the measurement of the transverse dimension (width) E-F.
The gallbladder volume was obtained using the volume calculation from the prolate ellipsoid formula (length x height x width x 0.523).\textsuperscript{15}

Gallbladder contractility index (GBCI) was calculated as percentage decrement of postprandial volume from the initial size, which is the percentage of fasting (V1) minus the postprandial (V2) gallbladder volume divided by the fasting (V1) gallbladder volume.\textsuperscript{15}

\[ \text{GBCI} = \frac{V1 - V2}{V1} \times 100\%. \]
DATA AND STATISTICAL ANALYSIS

The data collected (i.e. demographic data, fasting and postprandial gallbladder volume, calculated gallbladder contractility index, duration of DM) were analyzed using statistical software recharge for social sciences SPSS (version 16.0). Comparison between continuous variables such as age, duration of diabetes, gall bladder contractility index (ejection fraction) and prevalence of gall stone was performed by ANOVA or student’s t-test for unpaired values. Values with p<0.05 were considered significant.
LIMITATIONS OF THE STUDY

Ultrasonography is user dependent hence there may be minor variation in the values obtained. This will be minimized by taking all measurements thrice and obtaining the average.

Some of the recruited patients while waiting to be scanned complained of dizziness and were excluded from study as they have to eat, some never returned for post prandial evaluation of their gallbladder and finally challenges were met in identifying type II DM patients with neuropathy due to poor documentation.
ETHICAL CONSIDERATION.

Approval for the study was obtained from the ethical committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State.
RESULTS

In this prospective study, 100 diabetes patients were investigated with ultrasound. The ages of patient ranged from 44 years to 76 years with a mean average age of 59±11.73 years. Fifty diabetic patients with neuropathy were investigated with age ranged from 52 to 76 years and a mean age of 63.24±5.68 years. Fifty diabetic patients without neuropathy were also investigated with age ranged from 44 to 73 years with a mean age of 54.76±17.17. Fifty control subjects for age and sex match were also studied with age range from 44 to 80 years and a mean of 56.46±8.81. (fig.1). Forty four percent of diabetic group with neuropathy were male while 56% were females. In diabetic group without neuropathy and the control group male and female populations were equal in number (50% each). (Fig.2 &3.) All the investigated population shows no sign or symptoms of gall bladder disease.

Mean fasting gall bladder volume (FGBV) of diabetes with neuropathy in cubic centimetres (cm$^3$) was 37.74±16.9 SD, and that of diabetics without neuropathy was 29.14 ± 14.16 SD while that of the control group was 35.22 ± 16.75 SD. (Table 1 & fig.4&5).
FIG. 1: Bar chart showing mean age distribution in various groups.

Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
Fig. 2: Pie chart showing percentage sex distribution in diabetics patients with neuropathy (Group A).

Fig. 3: Pie chart showing percentage sex distribution in both diabetics without neuropathy and control groups (Group B & C).
The FGBV in diabetics with neuropathy was higher than in those without neuropathy and the difference was statistically significant (p-value = 0.007). The FGBV in diabetics with neuropathy is also higher than that of the control group but the difference was not statistically significant. (P- Value = 0.46). (Table 2).

The post prandial gall bladder volume (PPGBV) in cubic centimeter (cm³) revealed diabetics with neuropathy was 24.92±12.10 SD and in diabetics without neuropathy was 17.43±9.32 SD while that of the control group was 18.86±12.45 SD. (Table1 & fig.5)

The PPGBV in diabetics with neuropathy was higher than in diabetics without neuropathy and the difference was statistically significant (p-value =0.001).

The PPGBV in diabetics with neuropathy was also higher than that of the control group and was statistically significant with (p- value= 0.02). (Table 3).

The gall bladder contractility index (GBCI) in percentage was 33.44±13.62 SD in diabetics group with neuropathy;
Table 1: A table showing the mean Fasting Gall Bladder Volume (FGBV), Post Prandial Gall Bladder Volume (PPGBV) and Gall Bladder contractility index (GBCI) in various groups.

<table>
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<th>B (mean±SD)</th>
<th>C (mean±SD)</th>
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<td></td>
<td>N=50</td>
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<td>N+50</td>
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<tr>
<td>FGBV cm³</td>
<td>37.74±16.90</td>
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<td>PPGBV cm³</td>
<td>24.92±12.10</td>
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Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
Fig. 4: Box plot of mean gall volume and standard deviation showing out-layers in various groups.
Fig. 5: Bar chart comparing Fasting Gall Bladder volume and post prandial gall bladder volume in various groups.

Key:

Series 1: Fasting Gall bladder volume (FGBV)

Series 2: Post prandial Gall bladder volume (PPGBV)

Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
Table 2: A table comparing mean Fasting Gall bladder volume in various groups with test of significance.

<table>
<thead>
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<th>Serial Number</th>
<th>Study Group</th>
<th>FGBV (mean) cm³</th>
<th>P-value</th>
<th>Significance</th>
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Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
Table 3: A table comparing post prandial gall bladder volume (PPGBV) of various groups with fast of significance.

<table>
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<tr>
<th>Serial Number</th>
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<th>PPGBV (mean) cm³</th>
<th>P-value</th>
<th>Significance</th>
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Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
39.62±13.62 SD in diabetic group without neuropathy; while that of the control group was 47.68±18.01 SD. (Table 1, fig.6 & 7).

The GBCI is lower in diabetic group with neuropathy compare to those without, and the difference was statistically significant. (p-value=0.03). The GBCI is also lower in diabetic group with neuropathy than in the control population and the difference is statistically significant (p-value < 0.001) (Table 4).

The mean duration of diabetes in patients with neuropathy was 15.02±2.76 years and in diabetics without neuropathy was 5.67±3.13 years and this difference was statistically significant (p< 0.01). The relationship between FGBV and duration of diabetes shows a progressive linear correlation while that of GBCI and duration of diabetes shows regressive linear correlation. (Fig 8 & 9).

The prevalence of gall stone in all the diabetic patients investigated is 15%. The prevalence of gall stone among various groups shows that diabetics with neuropathy is 22%, compare with 10% and 8% for diabetic group without neuropathy and the control groups respectively. The prevalence is more in females in all the groups (Table 5).
Fig. 6: Bar chart showing gall bladder contractility index (GBCI) in various groups.

Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
Fig. 7: Box plot showing mean gall bladder contractility index and standard deviation with out-layers in various groups.
**Table 4:** A table showing Gall bladder contractility index (GBCI) in various groups with test of significance.

<table>
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<tr>
<th>Serial Number</th>
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<th>GBCI (%)</th>
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Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
Fig. 8: Scatter plot showing linear progressive relationship between gall bladder volume and duration of diabetes.
Fig 9: Scatter plot showing regressive linear relationship between duration of diabetes and gall bladder contractility
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<td>All diabetics</td>
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<td>8% (4)</td>
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<td>4% (2)</td>
<td>6% (3)</td>
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<td>Group C</td>
<td>0% (0)</td>
<td>8% (4)</td>
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**Table 5:** A table showing prevalence of gall stones in various groups

Group A: Diabetics with neuropathy

Group B: Diabetics without neuropathy

Group C: Control
DISCUSSION

The prevalence of diabetes mellitus is increasing worldwide and in Nigeria.\textsuperscript{2-4} The number of associated complications is also on the increase thus increasing the mortality and morbidity from this illness. Abnormalities in the gall bladder is one of the complications associated with long standing diabetes and strongly associated with diabetics with neuropathy.\textsuperscript{8-11} since most gall bladder abnormalities are usually clinically silent; ultrasonography is a useful tool in the assessment of the gall bladder in these patients since it is cheap, readily available carry no risk of ionizing radiation effect, as demonstrated in this study were it was used to evaluate 100 diabetes patients.

The age range of diabetes patients involved in this study was between 44 to 76 years with a mean age of 61 years. The control group were age and sex matched similar to what obtained in the study done by Sigh et al\textsuperscript{21} and Ertugrul et al\textsuperscript{34}.

In this study the FGBV is significantly higher in diabetics with neuropathy when compared to those without neuropathy. The FGBV in diabetics with neuropathy is also higher than in the control group though not significantly. This result is similar to what was obtained in the study done by Sigh et al\textsuperscript{21} which reveals FGBV in diabetics with neuropathy to be higher than those without, the difference though not statistically significant unlike in this study. FGBV in diabetics with neuropathy is significantly higher than in normal subjects though unlike in this study were the difference was not significant statistically. Increase FGBV seen in this study bears similarity with findings by Sharma et al\textsuperscript{22} which reveals subjects with neuropathy to have significantly larger fasting gall bladder volume. Gaul et al reveals diabetic patients had statistically significant larger FGBV and these values were highly significant amongst patients with autonomic
neuropathy. Other studies with this findings includes those of Guliter et al,\textsuperscript{25} Okoloba et al,\textsuperscript{27} Rupali et al,\textsuperscript{28} Chapman et al\textsuperscript{33} and Hahm et al.\textsuperscript{11} The increase FGBV in this study however is contrary to the findings by Keshavrzzian et al\textsuperscript{15} which reported that gall bladder dysfunction is rare.

The post prandial gall bladder volume (PPGBV) in diabetics with neuropathy is significantly higher than in those without neuropathy, and also significantly higher than those in the control group. This finding is similar to what is seen in a study by Ertugrul et al\textsuperscript{34} which revealed the average PPGB volume of gall bladder in diabetics with neuropathy to be significantly higher than the control group.\textsuperscript{34} Also in a study done by Gaul et al\textsuperscript{37} patients of diabetes mellitus have statistically larger post fatty meal gall bladder volume and these values were highly significant in patients with autonomic neuropathy. Other studies shows similar results when comparing diabetes with and without neuropathy as well as control.\textsuperscript{25-28}

The gall bladder contractility index (GBCI) which is a measurement of the ejection fraction in this study is seen to be significantly impaired in diabetics with neuropathy compare to the control group and also in diabetics without neuropathy. Similar findings were seen in the study by Sigh et al\textsuperscript{21} and Pazzi et al.\textsuperscript{9} The former author reported that GBCI was reduced in diabetics compare to control group; and further reduced in diabetics with neuropathy though not statistically significant. Guliter,\textsuperscript{25} Agarwal,\textsuperscript{26} Rupali,\textsuperscript{28} Soad,\textsuperscript{29} and Hahm et al\textsuperscript{32} in their various studies also demonstrated gall bladder ejection impairment in diabetics with neuropathy and control group. However Keshavrzzian\textsuperscript{15} and Sharma\textsuperscript{22} et al revealed normal gall bladder contractility in the various groups.
Diabetes tends to have larger FGBV, PPGBV, and reduced GBCI than control groups. Some of the reviewed studies did not show significant difference of these parameters in the various groups, this lack of significance difference between these groups could be due to the fact that in the controls, there was not only greater emptying but also greater refilling, so that the net volume change detected by ultrasound was relatively small.

The mean age of diabetic population with neuropathy is significantly higher than those of diabetic population without neuropathy in this study also the duration of the disease (diabetes) counted from the time of diagnosis is significantly longer in diabetes with neuropathy. This is consistent with the findings in the study done by Sigh and Olokoba et al. Sigh reported that autonomic neuropathy becomes more prevalent with increasing duration of illness while Okoloba reported the prevalence of gall stone disease to be a function of duration of diabetes.

Relationships thus exist between the duration of diabetes, FGBV, and GBCI. The mean FGBV is highest in the group that has the highest mean duration of diabetes; in this case the diabetic group with neuropathy. Whereas GBCI is lowest (reduced ejection fraction) in group with highest mean duration of diabetes disease that is diabetic group with neuropathy. Hence diabetic neuropathy becomes more prevalent with increase duration of illness. This finding was similar to that of Sigh et al. However Shawn et al did not find any correlation between the presence of neuropathy and impaired gall bladder contractility. Similarly Agarwal et al reported that gall bladder volume has no correlation with duration of diabetes.
Various studies have shown increase prevalence of gallbladder disease in diabetics, with higher prevalence observe in diabetics with neuropathy.\textsuperscript{21,23-25,27} This study reveals the prevalence of gall stone in diabetics generally to be 15% (fig.10). Diabetics with neuropathy have a higher prevalence over times two of that of the control group. Females have higher prevalence in all the groups. Similar findings were reported by Hahn et al\textsuperscript{11} and Olokoba et al.\textsuperscript{27}

The exact mechanisms for gall bladder dysfunction in diabetic patients are not known. Pazzi et al\textsuperscript{36} in a review of gall bladder motor function in diabetics proposed that the mechanism of gall bladder emptying abnormalities in diabetes mellitus 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. This needs to be further look into. Hahm s et al\textsuperscript{11} suggested that impairment of gallbladder motility complicated by autonomic neuropathy causes stasis and results in cholesterol gall stone crystal formation and gall stone growth. Some other studies further explain other proposed mechanism.\textsuperscript{38-50}
**Fig. 10:** Longitudinal sonogram showing stone in a gall bladder of a diabetic patient (white arrow).
CONCLUSION

Ultrasonography which is a very important imaging technique, cost effective with no side effect has shown to be very useful in the evaluation of gall bladder changes in patients with type II DM. From this study it was revealed that significant number of patients with type II DM has gall bladder abnormalities ranging from increase gall bladder volume to reduced ejection fraction (GBCI) with associated increase prevalence of gall stone disease. This is seen to be worse off in diabetics with neuropathy. Association also has been established between duration of diabetes and gall bladder abnormalities.
RECOMMENDATION

Ultrasonography of the gall bladder therefore is highly recommended in type II DM patient management especially in those with long duration of illness as this will aid proactive management of gall bladder complication which they are prone to, and reduce morbidity and mortality.
REFERENCES


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