Gall bladder volume and contractility in type 2 diabetes mellitus

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Abstract
The aim of this study was to sonographically evaluate gall bladder changes in type 2 diabetes. One hundred type 2 diabetic subjects (50 with neuropathy and 50 without neuropathy) and 50 healthy controls underwent sonographic evaluation of the gall bladder. Fasting and postprandial gall bladder volumes (FGBV and PPGBV) were measured, and the gall bladder contractility index (GBCI) calculated. The presence of gallstones was also noted. It was found that patients with diabetic neuropathy had a significantly higher FGBV and PPGBV, and lower GBCI, compared with diabetic patients without neuropathy; PPGBV and GBCI also differed significantly from non-diabetic controls. Gallstones were present in 22% of diabetic patients with neuropathy, in 10% of those without neuropathy, and in 8% of controls. We conclude that diabetic patients with neuropathy have significant abnormalities of gall bladder function, presumably due to autonomic nerve dysfunction. These patients also have a higher prevalence of gallstones, suggesting that ultrasound screening may be worthwhile.

Introduction
Diabetes mellitus is a syndrome of chronic hyperglycaemia due to relative insulin deficiency, resistance or both.1 At least 220 million people worldwide are affected by this disease, with a projected rise to 440 million by the year 2030.1 The chronic hyperglycaemia causes long-term damage to various body organs including the eyes, kidneys, nerves, heart, and blood vessels.2,3 The gall bladder is one of the organs that may be affected by autonomic neuropathy because vagal parasympathetic fibres maintain its tone and influence its emptying.4–6 An increased incidence of cholesterol gallstones, inadequate emptying, and increased volume have been reported as gall bladder changes associated with type 2 diabetes.5,7

The purpose of this study was to establish sonographic abnormalities in the gall bladder of type 2 diabetes patients in Nigeria, and to determine any correlation between these changes and duration of disease.

Patients and methods
This prospective, non-randomised, case-control study was carried out in the Radiology Department of a tropical university teaching hospital from March 2010 to January 2011. Informed consent was obtained from all the participants. The study group comprised 100 type 2 diabetic patients with and without clinical evidence of neuropathy (50 of each), as well as 50 healthy, age- and sex-matched, non-diabetic controls asymptomatic of gall bladder disease or other systemic illness that may affect the gall bladder. The subjects were recruited consecutively from the Endocrinology Clinic and ward of the hospital. Patients with type 1 diabetes, liver disease, or biliary disease were excluded. Diabetes was diagnosed according to American Diabetic Association criteria.8 The age, sex, and duration of diabetes of each subject were documented.

The presence of neuropathy was ascertained on physical examination by an endocrinologist. Autonomic neuropathy was tested for by taking the pulse rate at rest and repeating it while the patient performed a Vasalva manoeuvre. The subjects were then required to breathe normally and after a period of 5–10 minutes the pulse rate was taken again. The pulse rate is expected to normalise after this period to its resting state. Autonomic neuropathy was considered present when a subject had at least two abnormal cardiovascular reflexes, i.e. impaired heart rate response to Vasalva manoeuvre, standing, or deep inspiration. A postural fall in the systolic blood pressure of ≥30 mmHg when the patient changed from supine to an upright position also indicated autonomic neuropathy.9 Peripheral neuropathy was considered present when there was impairment of fine touch, pinprick sensation, vibration and position sense; or deep tendon reflexes. Based on these, the study subjects were divided into two groups: those without evidence of neuropathy and those with evidence of neuropathy. Fifty study subjects, consecutively recruited, were selected for these groups.

Abdominal ultrasonography was performed with a Mindray® DC-6 ultrasound machine (Shenzhen Mindray Bio-medical Electronics, Nanshan, Shenzhen, China) with a 3.5–5.0 MHz curvilinear transducer. Sonographic examination was performed after an overnight fast and repeated 45 minutes after ingestion of a fatty meal (bread and butter of about 40–50 g).

Each subject was scanned in the supine position. The transducer was placed longitudinally and beveled cephalad in the right hypochondrion to obtain the maximal
length (cm) and antero-posterior diameter (cm) of the gall bladder. The subject then turned to the left lateral decubitus position (oblique) to obtain the maximal transverse diameter (cm) of the organ by turning the probe transversely at 90° to the longitudinal plane. Each measurement was taken three times and the average obtained. The sonographic examinations were performed by one investigator to reduce inter-observer error.

The gall bladder volume (cm³) was then calculated using the prolate ellipsoid formula (length × height × width × 0.523). Gall bladder contractility index (GBCI) was the difference between the fasting and postprandial gall bladder volume (FGBV and PPGBV), divided by the fasting volume, multiplied by 100 (%). The study data were analysed using the Statistical Package for Social Sciences (SPSS) version 17 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean ± standard deviation (SD) and compared using analysis of variance (ANOVA) or Student’s t-test for unpaired values. Statistical significance was set at p<0.05.

Results

The mean ages of the diabetic patients with neuropathy, without neuropathy, and the controls were 63±6 years, 55±17 years, and 56±9 years respectively. Twenty-two (44%) of the neuropathic group were males, while 28 (56%) were females. The diabetic patients without neuropathy and the control groups had equal numbers of males and females (50% each).

Table 1 shows the FGBV and PPGBV, as well as GBCI for the three groups. The mean FGBV of Group A (diabetes with neuropathy) was significantly higher than Group B (diabetes without neuropathy), p=0.007. Similarly, PPGBV was higher in Group A compared with Group B (p=0.001), and also Group C (controls), p = 0.02. The GBCI was lower in Group A compared with Group B (p=0.03). It was also lower in the diabetics with neuropathy than those without neuropathy; Group C, controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>A (n=50)</th>
<th>B (n=50)</th>
<th>C (n+50)</th>
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</thead>
<tbody>
<tr>
<td>FGBV (cm³)</td>
<td>37.74±16.90</td>
<td>29.14±14.16</td>
<td>35.22±16.74</td>
</tr>
<tr>
<td>PPGBV (cm³)</td>
<td>24.92±12.10</td>
<td>17.43±9.32</td>
<td>18.86±12.45</td>
</tr>
<tr>
<td>GBCI (%)</td>
<td>33.44±13.62</td>
<td>39.62±15.15</td>
<td>47.68±18.01</td>
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</tbody>
</table>

Table 1. Mean fasting gall bladder volume (FGBV), postprandial gall bladder volume (PPGBV) and gall bladder contractility index (GBCI) in the study groups

Discussion

Gall bladder abnormalities may be seen in long-standing diabetes, especially those with diabetic neuropathy. Diabetes is also a known predisposing factor to emphysematous cholecystitis.

In this study, the FGBV was significantly higher in diabetic patients with neuropathy than in those without neuropathy (Table 1). The PPGBV with neuropathy was also higher than in the control group, though this was not statistically significant. Singh et al 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’s 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 Keshavrzian et al who also found that subjects with neuropathy had a significantly larger FGBV. However, our findings are at variance with the findings of Keshavrzian et al 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. Other studies also established a similar pattern among the three study groups.

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 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 and Agarwal et al also demonstrated gall bladder ejection impairment in diabetic patients with neuropathy.

The mean age of those with neuropathy was...
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.\textsuperscript{11}

The exact mechanisms for gall bladder dysfunction in diabetes patients are not known. Pazzi et al.\textsuperscript{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.\textsuperscript{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 utilise ionising radiation.

Author Declaration
Competing interests: none.

References