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The Association of Diabetes Mellitus with Cholelithiasis and Liver Diseases in Addis Ababa - Ethiopia

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Background: Gallstone disease is one of the most common gastrointestinal diseases reported in abdominal ultrasound investigations. Liver diseases and cholelithiasis are commonly linked with diabetes. Studies have shown that diabetic patients have a 2 to 3-fold increase in the incidence of cholesterol Gallstone. Our literature review indicated no similar study had been conducted in the country. This study was designed to determine the prevalence of diabetes mellitus on ultrasound diagnosed cholelithiasis and other liver diseases, amongst Ethiopians.
Methodology: A retrospective case control study was conducted at Myungsung Christian Medical Center (MCMC) on 250 cases with ultrasound evidence of cholelithiasis and 250 controls to determine the prevalence of diabetes mellitus and other liver diseases.
Results: A high prevalence of Diabetes mellitus was demonstrated among patients with gallbladder stones- 34% as compared to 15.2% in the controls (Pearson's chi-square 23.819, P value = 0.000, OR = 2.874). This association remained significant even when sex was controlled, though association was stronger among females.
Conclusions: The association observed in this study, between Diabetes mellitus and cholelithiasis among Ethiopians, may need wider scale study including dietary habits.

Introduction

Diabetes Mellitus and liver diseases including cholelithiasis are closely linked[1-3]. Individuals with diabetes mellitus are reported to have 2- to 3-fold increase in the incidence of cholesterol gallstones[4].DM is defined as a group of metabolic diseases whose common feature is an elevated blood glucose level[5]. In diabetic subjects, the biliary saturation index is increased and gallbladder motility is decreased[6]. Excessive glycogen and fat (fatty liver) deposition predisposes to cirrhosis and biliary disease. On the other hand, diabetes and abnormalities of glucose homeostasis occur as a complication of liver disease such as hepatitis C infection, hepatocellular carcinoma and cirrhosis[7]. Other risk factors include dietary pattern, blood lipid levels, high fat diet, body habits, age, sex, genetics, co-morbidities like cirrhosis and hemolytic diseases, and wide spread use of certain drugs[8-10].

In a case-control prospective study[11] done in Rome, Italy the prevalence of DM among age group 30-69 years, was found to be significantly higher than that of control group (11.5% versus 4.8% OR 2.55 (95% CI: 1.39-4.67). Results were the same even when sex was separately adjusted (18.3% versus 9.9% for men and 9.3% versus 2.6% for women)[11,12]. In another case-control study, an increased prevalence of gallstones (42%) in diabetic women could be demonstrated as compared to 26% in non-diabetic women[13]. Study reports from America and Japan had identified DM as a risk factor confined only to females [9, 12, 13], a situation attributed to sex hormones that cause increased cholesterol secretion and biliary stasis. The difference between women and men is particularly striking in young adults. The GREPCO study found a female-to-male ratio of 2.9 between the ages of 30 to 39 years; the ratio narrowed to 1.6 between the ages of 40 to 49 years and 1.2 between the ages of 50 to 59 years[12].

In Ethiopia, statistical audits for NCDs are not well established. A study conducted by Betre[14] (on 1436 youth of 15-24 years of age) in Addis Ababa, revealed a DM prevalence of 0.3%. It was reported that 2.6% & 3.3% of their mothers and fathers were also reported diabetics respectively.. Hospital based morbidity analysis revealed that cholelithiasis, is one of the commonest surgical problems in Addis Ababa[15].

It was the researchers' observation that, the number of DM patients with ultrasound evidence of Gall bladder stone was on the rise, although no survey reports so far could be found on the association between diabetes and cholelithiasis and other liver diseases in Ethiopian population. This study therefore, was conducted in an attempt to shade light by serving as baseline information for further studies. The investigators believe that such study results could possibly help in an endeavor to reduce the incidence of cholelithiasis in diabetic patients and the overall incidence of cholelithiasis and their management.

Patients and Methods

Study was conducted in Myungsung Christian Medical Center. MCMC is a specialized hospital with 85 beds that renders both outpatient and inpatient services. It has digital patient data base system in which all patient information including radiological investigations are filled. Approval for the study was obtained from the Research and Ethical Committee of the radiology department, faculty of Medicine Addis Ababa University and permission to use the hospital data was obtained from the medical director of the Center. For anonymity purposes, only card numbers were used to collect the data.

A retrospective case-control study was conducted using 18 months hospital records of a total of 500 patients with abdominal ultrasound scan evidence of cholelithiasis. All cases diagnosed to have cholelithiasis were taken and arranged sequentially based on their card number. Simple random sampling method was applied whereby every 5^{th} patient was taken as case; making a total of 250 cases. Equal numbers of patients who are next to the cases based on their card number and having no cholelithiasis were taken as controls. An inventory of patients' digital data base stored at the department of radiology of the MCMC was done. Then data was collected using a structured table which contains socio-demographic variables such as–age and sex and the last fasting serum glucose level determined. The abdominal sonography results were also evaluated for the presence of liver or GB diseases other than cholelithiasis.

Even though ultrasonography examination of the abdomen has not been conducted by a single radiologist, the tendency of observer measurement error affecting this study was minimal as only gross findings were used such as the presence of gall stone and major liver pathologies like fatty liver, Chronic Liver Disease and cirrhosis.

Data were collected, numbered and sorted out into cases and controls using checklist. Collected data were cross checked by principal investigator to ensure data quality. Data was entered, cleaned, and analyzed using SPSS version 11.0 soft ware. Descriptive statistics (such as means, frequency tables) were computed for most of the study variables. Numerical variables were categorized when needed for statistical manipulation. Study subjects were allocated in to two or more groups based on the suspected risk variable or factor and assessed for the presence or absence of cholelithiasis after coding them. When significant association was revealed, multivariate analysis was applied. Numerical variables such as age and Fasting Plasma Glucose were correlated and Pearson's correlation coefficient calculated. For categorical and continuous variables, chi-square and t-test were calculated too. P value less than 0.005 was regarded as statistically significant association.

Results

A total of 500 patients' records, 250 cases and 250 controls all above the age of 20 years were analyzed. The mean age for both groups was 50.08 years, ranging from 20 to 87 years and Standard deviation of 14.2. The mean ages of females and males were 49.34 and 51.93 years respectively. The mean age of the cases and controls were 51.75 and 48.42 years respectively. Cases were older and there was a statistically significant difference between both groups, (t-value -2.6, (-5.816 - -0.856) and

P value= 0.008). Majority of the subjects (73.4%) were in the age group 40 years and above and those 60 years and above accounted for about one third (30%).

Among the 500 study subjects, 143 (28.6%) were males and the rest 357 (71.4%) were females. Among the cases group, 191 (76.4%) were females and for the control group was 59(66.4%) (Figure 1). The mean FPG was 116.7mg/dl with a SD of 50.839 (among males: 134.65 mg/dl. with SD of 68.154 among females: mean 109.52 mg/dl. with SD of 39.86). A statistically significant difference between the means was revealed. (t-value = 5.12, P value = 0.000). The mean for the cases and control groups were 124.83 and 108.58 mg/dl respectively, with significant difference between the groups (t-value = 3.617, P-value = + 0.000). One hundred twenty three of the samples, accounting for 24.65 fulfilled the criteria for the diagnosis of DM. About two third of them had FPG less than 111 mg/dl (Table 2).

Twenty four (24) of the sample population had one or another form of liver disease. 2/3 of them had fatty liver (62.5%), 8(33.3%) had chronic liver disease and single patient had hepatitis. Seventy nine percent of those with liver disease other than cholelithiasis had also DM. The overall prevalence of DM was 24.6% (123/500), with 34 %(85/250) and 15.2 %(38/250) among cases and control groups respectively. Thus, DM was found to be strongly associated with cholelithiasis. (Pearson's chi-square 23.819, P value= 0.000). Those with DM were 3 folds at risk of developing cholelithiasis (OR = 2.874) (Figure II). When the association was further stratified by sex, about a quarter of the females in the case group had DM as compared to below 10% in the controls. With regards to male sex, fifty percent of the males in the case group had DM which is twice as that of the controls. DM and cholelithiasis remained to be significantly associated even when stratified by sex with stronger association among females (Table 3). When stratified by age, the association between DM and cholelithiasis was statistically significant for those aged 40 and above -41.5% (80/193) of the Cases but 19.5 (34/174) among the controls. (Table 3).

Table 1. Age distribution of cases and controls

Age	Patients with cholelithiasis Number (%)	Patients without cholelithiasis Number (%)	Total Number (%)
20-29	13(5.5)	15(6.0)	28(5.5)
30-39	44(17.6)	61(24.4)	105(21.0)
40-49	52(20.8)	57(22.8)	109(21.8)
50-59	55(22.0)	53(21.2)	108(21.6)
60-69	54(21.6)	46(18.4)	100(20.0)
70-79	24(9.6)	15(6.0)	39(7.8)
80-89	8(3.2)	3(1.2)	11(2.2)
	Using cutting point of 40 yrs		
40+	193(77.2)	174(69.6)	367(73.4)
< 40	57(22.8)	76(30.4)	133(26.6)
Total	250	250	500

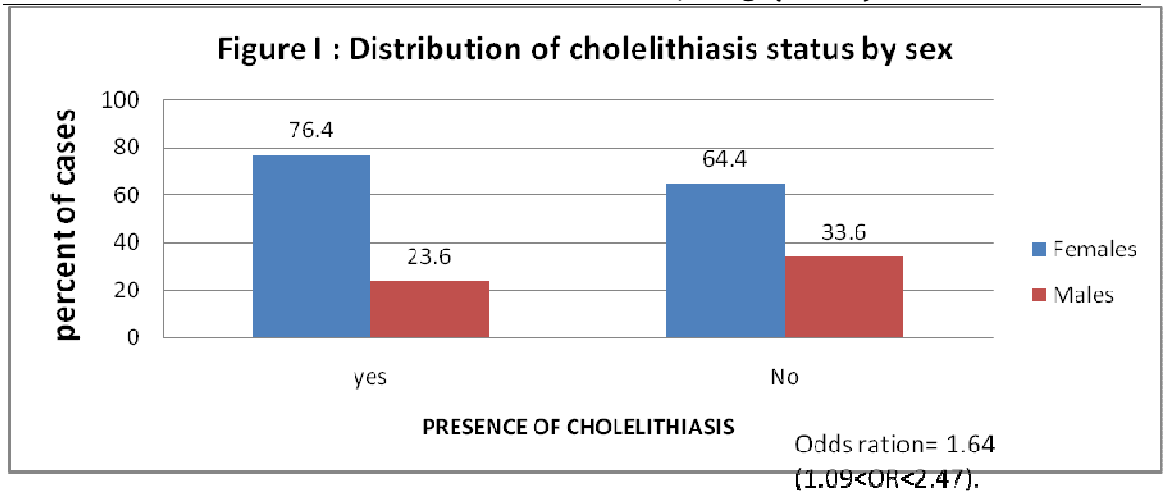

Table 2. Fasting Plasma Glucose Distribution of Cases and Controls

FPG Img/dl)	Total N (%)	Cumulative total N (%)
Less than 110	327 (65.4)	327 (65.4)
111-125	50(10.0)	377(75.4)
126-140	30(6.0)	407(81.4)
141-160	32(6.4)	439(87.8)
161-180	12(2.4)	451(90.2)
181-above	49(9.8)	500(100)

Males: Pearson's chi-square=7.137, P value = 0.007, Females: Pearson's chi square=23.6161, P value = 0.000. For age group less than 40: Pearson's chi-square 0.369, P value = 0.497
For age group 40 and above: Pearson's chi-square=20.514, P value = 0.000)

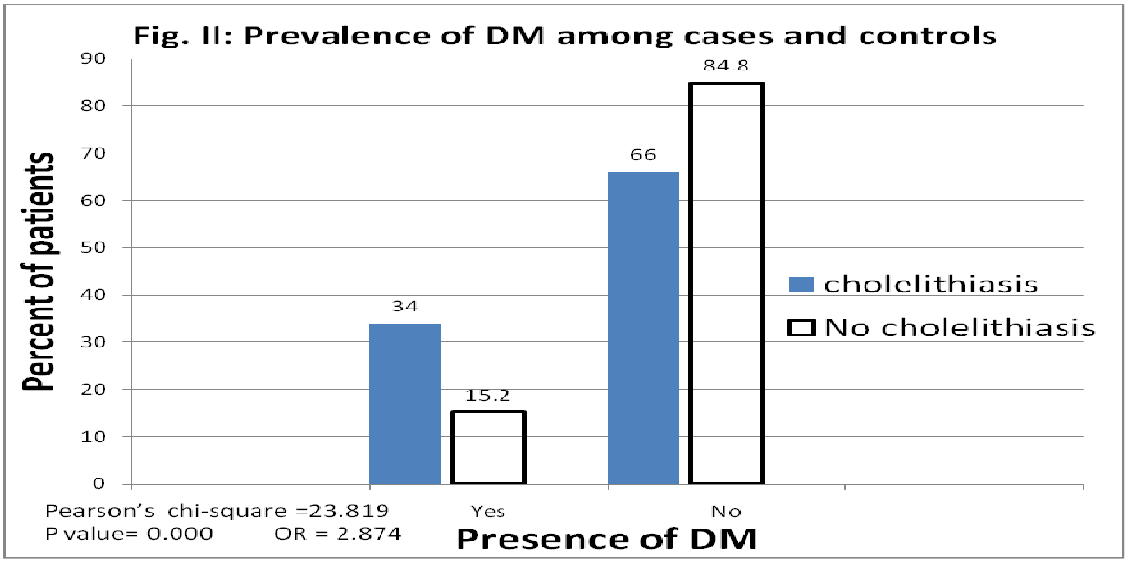

Figure 2

Table 3. Prevalence of DM in Cases and Controls, Stratified by Age and Sex

Presence of DM	Males		Females	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Yes	30(50.8)	24(28.6)	55(28.8)	14(8.4)
No	29(49.2)	60(71.4)	136(71.4)	152(91.6)
Total	59	84	191	166
	Age less than 40yrs		**Age 40yrs and above**	
Yes	5(8.8)	4(5.3)	80(41.5)	34(19.5)
No	52(91.2)	72(94.7)	113(58.5)	140(80.5)
Total	57(100)	76(100)	193(100)	174(100)

Table 4. Status of liver disease excluding cholelithiasis and DM among the sample population

Presence of DM	***Liver disease excluding cholelithiasis***		
	Present N (%)	Absent N (%)	Total
Yes	13(10.57)	110(89.43)	123(100)
No	11(2.92)	366(97.08)	476(100)

Pearson's chi-square= 11.882; P value = 0.002 Odds ration =3.93(1.6<OR<9.72)

DM and liver disease (excluding cholelithiasis):
About 11% of the diabetics had also liver diseases other than cholelithiasis but only about 3% among the non diabetics had liver disease other than cholelithiasis. The prevalence of DM among those with liver disease was 54.2% as compared to 23.1% among those without liver disease (after excluding cholelithiasis in both cases). This association was statistically significant. (Table 4).

Among the cases 7.6% had also liver conditions other than cholelithiasis, while only 2.0% of the control group had similar problem (Pearson's chi-square 8.578, P value 0.005) those with liver disease (excluding cholelithiasis) were about 4 folds more likely to have cholelithiasis. The occurrence of cholelithiasis tended to increase as age increased. The prevalence of cholelithiasis was 22.8% in the age group 20-29, 17.6% in the age group 30-39, 20.8% in the age group 40-49, 22.0% in the age group 50-59 and 34.4% in the age group 60 and above. (Table 1).

Discussion

Findings of this study include the strong association between DM and cholelithiasis with high prevalence of DM among both cases and control group (34% and 15.2%). The risk of developing cholelithiasis among diabetics was found to be three times more compared with non- diabetics [4]. This finding is consistent with a study done by Adriano et al [10] in Italy in which the prevalence was 2.4 times higher. But the prevalence of DM among cases and controls was (8.9% & 4.3%) were much lower when compared with the results of the present study [(11).] This figure is even higher than a similar study (provider-based) conducted in Bulgaria [(7).] This discrepancy may be ascribed to difference in methodology that encompasses the following: 1) provider-based rather than population based design tends to yield higher figures. 2) Differences in definitions applied- this study used the revised definition on DM a FPG greater than 140mg/dl and /or oral glucoses tolerance test, others used the older definition[5].

The association between DM and cholelithiasis remained to be significant even after controlling sex, though the association was stronger among females. But in the case of age, it was limited to older age (age 40 and above years) similar with a study conducted in Rome. Those with liver diseases other than cholelithiasis were also at higher risk of having DM with increased age[14]. Cholelithiasis was

found to increase as age increased[11, 12]. Regarding sex and cholelithiasis, a statistically significant gender difference was noted in which females were 1.6 times more at risk, a finding concordant with other studies from Spain and France [2, 13].

Liver diseases such as cirrhosis are known risk factors for the development of cholelithiasis. Even after the effect of liver diseases other than cholelithiasis was controlled, a statistically significant association was observed between DM and cholelithiasis. Since those with liver diseases other than cholelithiasis were small in number, they were grouped in one and had 4 folds more likely to have cholelithiasis[1-3].

The study showed a strong association of DM with cholelithiasis. As confirmed by various studies, DM is thought to contribute to cholelithiasis through two mechanisms: gallbladder mobility abnormalities related autonomic neuropathy and secretion of lithogenic bile.

Conclusion

Based on the findings, we conclude that Diabetes is a likely risk factor for acquiring cholelithiasis in Ethiopians. From our literature review it was evident that no similar research has been conducted in Ethiopian population, hence, this research report will serve as baseline information for larger scale subsequent studies.

Recommendation

Improve service statistics will avoid paucity of data, as information collected on risk factors for cholelithiasis obtained from routine hospital data can allow researchers to reach to plausible conclusions with minimal resources.

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