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RESEARCH ARTICLE

Gallbladder dysfunction and gallstone prevalence in patients with chronic kidney disease. Is there a difference between predialysis and hemodialysis patients? A multi-center Study.

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Manuscript Info *Abstract*

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Background: Gallbladder stone formation is undoubtedly multifactorial, and many related factors had been thoroughly investigated. We evaluated gallbladder function and gallstone prevalence in chronic kidney disease (CKD) patients and compared them among predialysis (PreD) and hemodialysis (HD) patients. **Methods:** A Cross-sectional controlled study was carried out in three big tertiary hospitals. Three groups of subjects were enrolled in the study; 100 control subjects, 120 PreD patients, who had CKD stage 4 and 5, and 135 CKD patients on regular HD. Routine biochemical parameters were assessed in all subjects. Ultrasonography was done for all groups to evaluate gallbladder volumes, and ejection fraction (EF) was calculated. **Results**: Gallbladder fasting volume (FV) was significantly different among study groups. There were statistically significant differences between CKD patients and controls, regarding both gallbladder residual volume (RV) and EF (*P=0.008* and *P<0.001*, respectively). However, no statistically significant differences were found between PreD and HD patients, regarding both gallbladder RV and EF. Regarding, the frequency of gallbladder stones, there was a statistically significant difference between CKD patients and controls (*P<0.004*). **Conclusion:** CKD is associated with significant gallbladder dysfunction and high gallstone prevalence, however, these changes did not differ significantly between PreD and HD patients.
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Introduction

The prevalence of gallbladder diseases is variable among adults in developed and developing countries. In addition, it is considered as an important risk for morbidity such as cholecystitis, cholangitis and pancreatitis.[1-2]

Gallstones affect 10% to 15% of the adult population in developed countries.[2-3] Scanty of epidemiologic studies have reported the prevalence of gallstone disease in Middle East countries; ranging between 4 to 12% of general population.[4-7]

There are many known risk factors for gallstone formation, of which, the most important non modifiable factors are reported to be ethnic background, increasing age, female gender, family history and genetics. The modifiable

risks for gallstones are obesity, rapid weight loss and a sedentary lifestyle. Risk factors for biliary sludge include pregnancy, drugs like ceftiaxone, octreotide and thiazide diuretics, and total parenteral nutrition or fasting. Diseases like cirrhosis, chronic hemolysis and ileal Crohn's disease are risk factors for black pigment stones.[1-2,8-9]

Whether chronic kidney disease (with or without dialysis) is associated with an increased risk of gall bladder disease is still debatable. Some studies reported higher prevalence of gallstones in patients with chronic kidney disease (CKD),[10-11] whereas, the others reported no difference from general population.[12-15]

The most important factors in the pathogenesis of gallstones are the lithogenic composition changes of bile, increased nucleation tendency, and impaired motility of gallbladder.[3] It has been reported that CKD patients on regular hemodialysis (HD) have increased bile cholesterol levels and an increased bile saturation index.[13] Low-protein diet has been administered to some patients with chronic renal failure, and in animal studies, this diet has been shown to alter the composition of bile, favoring cholelithiasis.[16] In addition, the gallbladder is innervated by the autonomic nervous system, which malfunctions in uremia, and it has been shown that gallbladder stasis might cause increased stone formation.[17-18]

Therefore, we investigated patients with CKD either in predialysis (PreD) state or maintained on HD for prevalence of gall bladder dysfunction and gallstone disease in comparison to healthy individuals.

SUBJECTS AND METHODS:

This cross sectional survey study was done in the period between June 2013 and May 2014, at three big tertiary hospitals; Zagazig University Hospital, Zagazig, Egypt, as well as King Abdulaziz Hospital, Jeddah, and Royal Commission Medical Center (RCMC), Yanbu, both in Saudi Arabia. The study entitled a total of 255 CKD patients and 100 control individuals who were apparently healthy relatives of our patients and were matching the patients as regard; gender, age, body mass index (BMI) and nationality. All patients and control individuals had the same Arabian ethnic background. We classified all participants in this study into three groups; ***group 1***included the control individuals (n = 100), ***group 2*** included the PreD patients, in stage 4 and 5 according to the CKD classification[19] (n = 120) and ***group 3*** included the CKD patients on regular HD (n = 135).

Participants with conditions known to affect gallbladder motility were excluded from the study. These included subjects below the age of 18 years or above 60 years, pregnant women, those who were using drugs that might affect gallbladder functions, those who had diabetes mellitus or chronic liver disease, and those with a history of cholecystectomy. We did not include patients on peritoneal dialysis due to their scanty number in our centers.

The study was approved from the ethics committees in the hospitals before enrolment. All participants were interviewed and informed about the study rationale and aim. Informed consent was signed by each participant prior to enrollment to the study.

All participants in study groups underwent thorough clinical evaluation, blood chemistry analysis and abdominal ultrasonography and calculated body mass index (BMI). Blood chemistry including, fasting blood glucose (FBG), blood urea nitrogen (BUN), creatinine, calcium, phosphorus, parathormone (PTH), total protein, albumin, cholesterol, and triglycerides were assessed in all groups just before the study. In the HD group, blood samples were taken just before HD in the first session of the week.

Three experienced radiologists (one in each hospital) performed the ultrasonographic (US) examinations for all subjects, using a 3.5-MHz convex transducer. Gallbladder volume (ml) was measured by the sum of cylinders method.[20]Ultrasonographic scanning was performed after 10 hours overnight fasting to ensure adequate gallbladder distension. The maximum length, width, and height of the gallbladder were measured in fasting individuals and 30 min after a standard meal consisting of 100 g chocolate (55.9% carbohydrate, 33.1% lipid, 7.6% protein). This procedure was performed twice for every participant with one week interval, by the same radiologist. The averages of gallbladder volumes in both occasions was calculated and considered in the results. The study participants remained in the sitting position after meal and between scans to facilitate passage of the meal through the stomach to the duodenum. Images and measurements were obtained in suspended deep inspiration. Fasting gallbladder volume was designated as fasting volume (FV), whereas the volume achieved 30 min after the meal was considered the residual volume (RV). Gallbladder ejection fraction (EF) was calculated by the following formula; $EF = (FV - RV) / FV \times 100$. In addition, the common bile duct caliber was measured and the presence of gall stone(s) was recorded.

Statistical Analysis

Results are expressed as means ± SD (standard deviation) for continuous variables, while counts and percentages for categorical variables. Comparison between two independent mean groups for parametric data were performed using

Student's t-test and Chi-square test was used to compare categorical variables. The significance level for all statistical two-tailed tests were accepted as $P < 0.05$.The statistical analyses were conducted using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA).

RESULTS:

The demographic analysis of CKD patients (PreD, HD) and controls showed no significant difference as regard age, BMI, gender and nationality distribution (table 1). Results of some laboratory investigations showed significant differences among the study groups, including, BUN, creatinine, calcium, phosphorus and PTH, while, no significant differences were found among the study groups regarding other laboratory results (table 2).

Table 1: Differences in demographic features, among study groups.

Variable	Group 1 Controls (n=100)	Group 2 PreD(n=120)	Group 3 HD (n=135)	Groups 2+3 Pre & HD (n=255)	P^1	P^2	P^3	P^4
Age	46.22±8.39	47.15±6.74	48.50 ±10.26	47.83±8.5	NS	NS	NS	NS
Gender (no. & %)								
Males	51 (51%)	63 (52.5%)	70 (51.8%)	133 (52.2%)	NS	NS	NS	NS
Females	49 (49%)	57 (47.5%)	65 (48.1%)	122 (47.8%)	NS	NS	NS	NS
BMI (kg/m^2)	23.85 ±4.30	23.34±3.17	22.88±4.12	23.14±3.25	NS	NS	NS	NS
Nationality (no. & %)								
Egyptian	50 (50%)	64 (53.3%)	68 (50.3%)	132 (51.8%)	NS	NS	NS	NS
Saudi	50 (50%)	56 (46.7%)	67 (49.7%)	123 (48.2%)	NS	NS	NS	NS

P^1: PreD vs. control, P^2: HD vs. control, P^3: PreD and HD vs. control, P^4: PreD vs HD. NS: not significant. $P < 0.05$ is significant.

Table 2: Differences in blood chemistries, among study groups.

Variables Mean±SD	Group 1 Controls (n=100)	Group 2 PreD(n=120)	Group 3 HD (n=135)	Groups 2+3 Pre & HD (n=255)	P^1	P^2	P^3	P^4
FBG (mg/dl)	90.86±8.66	90.70±8.53	92.56±10.92	91.63±11.96	NS	NS	NS	NS
BUN (mg/dl)	17.28±3.89	72.43±19.04	83.15±24.35	77.79±22.02	<0.001	<0.001	<0.001	<0.001
Creatinine (mg/dl)	0.96±0.31	5.13±1.92	10.95±1.89	8.54±2.33	<0.001	<0.001	<0.001	<0.001
Calcium (mg/dl)	9.85±0.78	8.43±1.06	9.05±0.79	8.74±0.96	<0.001	<0.001	<0.001	<0.001
Phosphorus (mg/dl)	3.57±0.57	5.97±1.76	5.67±1.41	5.77±1.57	<0.001	<0.001	<0.001	NS
PTH (pg/ml)	42.61±14.59	183.18±32.37	480.22±94.47	331.69±74.7	<0.001	<0.001	<0.001	<0.001
Albumin (g/dl)	4.01±0.67	3.9±0.74	3.85±0.64	3.88±0.68	NS	NS	NS	NS
Total Protein (g/dl)	7.33±0.52	7.17±1.15	7.25±1.02	7.18±1.07	NS	NS	NS	NS
Cholesterol (mg/dl)	193.69±27.36	190.55±52.73	201.46±37.07	195.5±49.24	NS	NS	NS	NS
Triglyceride (mg/dl)	178.62±37.69	170.98±47.66	184.46±66.01	177.72±56.65	NS	NS	NS	NS
LDL (mg/dl)	111.27±27.25	106.09±54.72	115.93±39.77	111.51±47.24	NS	NS	NS	NS
HDL (mg/dl)	46.69±8.84	48.26±9.24	45.64±11.33	46.95±10.28	NS	NS	NS	NS

P^1: PreD vs. control, P^2: HD vs. control, P^3: PreD and HD vs. control, P^4: PreD vs HD.

Gallbladder FV was significantly different among study groups (table 3). There were statistically significant differences between CKD patients (groups 2 and 3) and controls, regarding both gallbladder RV and EF (10.81±4.71 ml vs 9.27±5.01 ml, *P=0.008*, and 56.08±14.24% vs 67.51±12.08%, *P<0.001*, respectively) (table 3). However, no statistically significant differences were found between PreD (groups 2) and HD patients (group3), regarding both

gallbladder RV and EF (11.44±5.89 ml vs 10.38±4.33 ml, and 57.20±17.05% vs 54.97±11.47%, respectively) (table 3). Regarding the frequency of gallstone disease encountered in this study, there was a statistically significant difference between CKD patients (40 cases, 15.6%) and controls (4 cases, 4%) *(P<0.004)*. (table 3). Moreover, a negative relation was found between the means of gallbladder EF and frequencies of gallstone disease, among different study groups (figure1).

Table 3: Differences among all study groups regarding GB functions and cholelithiasis.

Variables	Group 1 Controls (n=100)	Group 2 PreD(n=120)	Group 3 HD (n=135)	Groups 2+3 Pre & HD (n=255)	P^1	P^2	P^3	P^4
FV (mL)	28.79±11.16	27.56±10.93	22.98±6.32	25.27±9.01	NS	<0.001	0.002	<0.001
RV (mL)	9.27±5.01	11.44±5.89	10.38±4.33	10.81±4.71	0.004	NS	0.008	NS
EF (%)	67.51±12.08	57.20±17.05	54.97±11.47	56.08±14.24	<0.001	<0.001	<0.001	NS
Gallstone (no.&%)	4 (4%)	19 (15.8%)	21 (15.55%)	40 (15.68%)	S	S	0.004	NS

P^1: PreD vs. control, P^2: HD vs. control, P^3: PreD and HD vs. control, P^4: PreDvs HD.

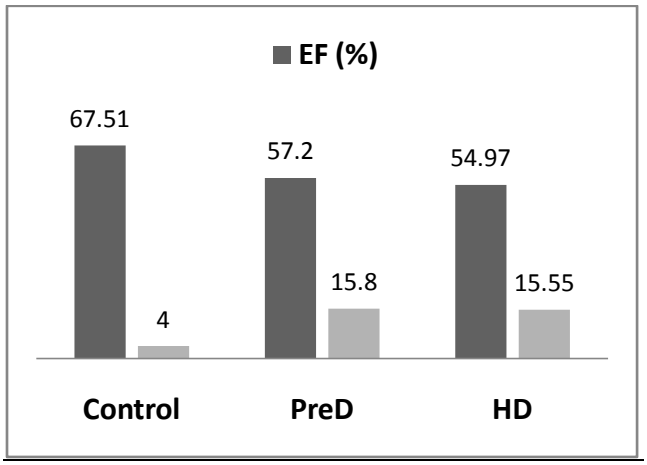

Figure 1: Relation between gallbladder EF and presence of gallbladder stone(s), among different study groups.

DISCUSSION:

The prevalence of gallstones in patients with CKD ranges widely between 3.85% to 27.8%.[10-15,21] Some abnormalities related to CKD predispose to gallstone formation.[1]Autonomicdysfunction is frequent in CKD patients,[22]and impairs gallbladder motility predisposing to gallstone formation.[17-18] The lithogenicity of bile increases in CKD due to an increase in bile cholesterol, a decrease in primary and an increase in secondary bile acids in the bile, and an increased saturation index of bile.[13,23] These changes are further enhanced by the effect of a low-protein diet and predispose to gallstone formation.[16]

We carried out this multicenter study on 132 Egyptian and 123 Saudi patients with CKD (distributed as 120 PreD patients and 135 HD patients) as well as 100 healthy control individuals, to assess gallbladder function especially motility which is one of the most important factors that may affect gallstone formation. There were no significant differences regarding demographic features among PreD patients, HD patients and controls in our study. Some blood chemistries were significantly altered in patient groups due to the nature of their disease, including, BUN, creatinine, calcium, phosphorus and PTH, while, no significant differences were found among the study groups regarding other biochemical parameters including lipid profile.

Gallbladder FV did not differ significantly between control group and PreD group, however, it was significantly lower in HD group. There were statistically significant differences between all CKD patients (groups 2 and 3) and controls, regarding both gallbladder RV and EF (*P= 0.008* and *P<0.001*, respectively). However, no statistically significant differences were found between PreD and HD patients, regarding either gallbladder RV or EF.

Wang et al., (1996)[24] had studied the motility of gallbladder in 22 patients with CKD and 17 normal subjects. In agreement with our results, *Wang et al., (1996)* showed significantly smaller gallbladder FV in CKD patients than in normal subjects (P<0.01). However, in disagreement with our results, they reported no significant difference of the maximal percentage of gallbladder emptying (EF) between CKD patients and normal subjects. This disagreement may be explained by the small number of patients included in their study. Moreover, in disagreement with our results, *Gladziwa et al., (1993)*[12] *and Altiparmak et al., (2003)*[15]reported lack of differences in gallbladder function (EF) between CKD patients and normal subjects. In both studies, gallbladder function was compared between HD patients and controls. On the other hand, in our study we compared gallbladder function between CKD patients (both PreD and HD patients collectively) and healthy populations.

Gastrointestinal manifestations in patients with CKD were frequently reported and attributed to impaired gastric motility due to autonomic nervous system dysfunction.[25-26] Similarly, the presence of significant alteration of gallbladder function (RV and EF) in our CKD patients, may be due to autonomic dysfunction,with or without other neuronal and hormonal mechanisms related to CKD e.g. increased serum gastrin.[15]

Furthermore, going with reports of previous studies,[10-11,21] we observed a significantly increased frequency of gallstones in PreD and HD patients compared to control group *(P=0.004)*. Whereas, reports of others studies showed no difference from general population.[12-15] The negative relation between gallbladder EF and frequency of gallstone disease, among different groups in our study (figure 1) was consistent with the findings of *Pauletzki et al., (1996)* who reported that gallbladder emptying is an important factor in the formation of recurrent gallstones.[18] Also in agreement to our results, *Gençtoy et al.,* have reported in 2014, an increased frequency of gallbladder stones in hemodialysis patients.[27]

There were some limitations of this study. The first was that the ultrasonographic examinations are operator dependent, so to overcome this problem, ultrasonographic examination were repeated. Secondly, This was a hospital-based study and may not be able to be extrapolatedto the general population. Finally, there was a retrospectivereview of medical records, and there was the potential formissing some confounders, e.g., family history ofgallstone disease, number of pregnancies, oral contraceptiveuse, and menopause were not always mentioned in themedical records.

In conclusion, CKD is associated with significant gallbladder dysfunction and high gallstone prevalence, however, these changes did not differ significantly between PreD and HD patients.

CONFLICTS OF INTEREST:

No potential conflict of interest relevant to this study was reported.

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