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Increased frequency of gallbladder stone and related parameters in hemodialysis patients

BILIARY

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Original Article

ABSTRACT

Background/Aims: The prevalence of gallbladder stone (GBS) is shown to be increased in some studies in patients with chronic kidney disease (CKD). Nevertheless, some other studies did not confirm these findings. The controversial results about the prevalence of GBS in hemodialysis (HD) patients demand new studies to search GBS prevalence and associating risk factors in HD patients. In the present study, we aimed to investigate GBS prevalence and risk factors in our HD patients.

Materials and Methods: A total of 104 HD and 149 control patients were involved. Complete physical examinations, including measurements of dry body weight and height, were done. Abdominal ultrasonography was conducted by the same experienced radiologist. Blood samples were drawn via venipuncture from the study participants after they had fasted overnight just before a midweek hemodialysis session for laboratory examinations.

Results: The prevalence of GBS in HD patients was 34.6 % (36/104), and that was significantly higher than that of control group 12.9% (17/149; p=0.0001). In all study participants (HD patients and control group), patients with GBS were older than patients with no GBS (63.2±14.2 vs 53.7±16.7; p=0.0001). However, in HD patients, mean age was similar in patients with GBS and no GBS (64.3±13.8 vs 60.1±16.6; p>0.05). Patients with GBS had a higher prevalence of units of blood transfusions than patients with no GBS in hemodialysis patients (2.0±2.9 vs 0.9±1.3; p=0.047)

Conclusion: The present study showed an increased prevalence of GBS in HD patients compared to healthy controls. The number of blood transfusions and autonomic neuropathy may be responsible for the increased prevalence of GBS in HD patients.

Keywords: Hemodialysis, gallbladder stone, blood transfusion

INTRODUCTION

Cholelithiasis is one of the most common gastrointestinal problems that lead to enhanced morbidity, mortality, hospital stay, and large expenses. Surgical treatment may not be needed except for the presence of pain or complications, such as cholecystitis, cholangitis, jaundice, or pancreatitis (1). It has a prevalence of 10-20% in adult populations (2). In patients with chronic kidney disease (CKD), the prevalence of gallbladder stone (GBS) is shown to be increased with the advancement of disease stage, from 7.7% in CKD stage 1 to 21.3% in CKD stage 5 (3). Studies in dialysis patients showed a wide range of prevalence of GBS between 3.85%-33.3% (4,5). On the other side, it is unclear whether the prevalence of GBS is increased in hemodialysis patients. Numerous studies revealed an increased prevalence of biliary lithiasis in hemodialysis (HD) patients compared to the healthy population (2,3). However, others reported similar incidences with normal populations (4,6-9). Besides the risk of complications, patients on dialysis treatment with asymptomatic GBS would have more severe complications related to GBS after transplantation (10). So, it is important to determine

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GBS in HD patients who are candidates for renal transplantation whether they are asymptomatic.

In otherwise healthy populations, some important risk factors have been identified as being associated with gallstones. These include ethnicity, family history and genetics, increased age, female gender and sex hormones, obesity, dyslipidemia, diabetes mellitus, metabolic syndrome, rapid weight loss, diet and total parenteral nutrition, lifestyle factors and socioeconomic status, and underlying chronic diseases (Crohn disease, liver disease, cystic fibrosis, sickle cell disease, and other chronic hemolytic diseases and certain drugs) (ceftriaxone, octreotide, and thiazide diuretics). Secondary hyperparathyroidism, diabetes mellitus, and increased phosphorus levels were shown to be related with increased prevalence of GBS in HD patients (2,5,11,12). Current knowledge is not enough to say that hemodialysis itself is a risk factor for GBS formation; however, the studies showing increased prevalence of GBS in HD patients demand new studies to search GBS prevalence and associating risk factors in HD patients.

In present study we aimed to investigate gallbladder stone prevalence in our hemodialysis patients and compare with age and sex matched healthy population. We also investigated the risk factors associating existence of GBS in hemodialysis patients.

MATERIALS AND METHODS

A total of 104 out of 149 hemodialysis patients (61 men, 43 women, mean age: 56.9±15) were included in the study. Patients were selected from our hemodialysis unit after elimination of exclusion criteria. Oral and written informed consents were taken from all study participants. The study is approved by the local ethics committee of Başkent University Faculty of Medicine.

Exclusion criteria

Patients with chronic liver disease, morbid obesity (BMI>40), chronic inflammatory bowel disease, chronic hemolytic anemia (sickle cell disease, thalassemia, or other), or a history of medications, including octreotide, thiazide diuretics, and ceftriaxone, were excluded from the study.

All patients were on regular 4-hour bicarbonate hemodialysis with the same hemodialysis machines (NIKKISO-DB05; Japan) and same membranes (Polysulphone; 1.6-2 m^2; AllMed GmbH; Germany). Data, including age, sex, demographic data, time on dialysis, primary renal diseases, history of systemic diseases (diabetes, chronic obstructive pulmonary disease, coronary artery disease) and gastrointestinal surgery, current medications and drugs used in the last two years, total number of childbirths, and use of oral contraceptives in females, were collected from hemodialysis data sheets and oral interviews with patients. Complete physical examinations, including measurements of current dry body weight and height, were done. Body mass indexes were calculated using these data. Ultrasonography of the abdomen was conducted by the same experienced radiologist using a scanner equipped with a 3.5-MHz transducer (Esaoate/Biomedica AU3; 3.5/5 MHz). Blood samples were drawn *via* venipuncture from the study participants after they had fasted overnight just before a midweek hemodialysis session by clinical nurses for the laboratory examination. Fasting plasma glucose (FPG), triglyceride, total cholesterol (TC), high-density-lipoprotein cholesterol (HDL-C), and low-density-lipoprotein cholesterol (LDL-C), were measured using a Hitachi Modular analysis system (Roche Modular DPP, Hitachi Ltd, Tokyo, Japan). Calcium, phosphorus, BUN, creatinine, intact parathyroid hormone, serum iron, total iron binding capacity, ferritin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total and direct bilirubin, uric acid, total protein, and albumin levels were also studied. Intravenous or oral iron, erythropoietin treatments, and number of units of blood transfusions were recorded from the last year's hemodialysis records.

Control group

A total of 149 age- and sex-matched volunteers were used as the control group. Volunteers were chosen among our hospital workers and patients admitted to the internal medicine clinic for hypertension, urinary system infection, headache, common cold, and other upper respiratory tract infections (patients admitted for obesity, gastrointestinal/liver diseases, dyslipidemia, and hemolytic anemia were not included). Oral informed consent was provided from all volunteers and patients included in the study. Study was performed in accordance with the principles of the Declaration of Helsinki (13). All participants were questioned for chronic/active diseases, family or self-history of gallstones, current medications (oral contraceptives or other drugs), and number of pregnancies and childbirths for women. In the control group, ultrasonography of the abdomen was conducted by the same experienced radiologist using a scanner equipped with a 3.5-MHz transducer (Esaoate/Biomedica AU3; 3.5/5 MHz). Complete physical examinations, including measurements of current body weight and height, were done. Body mass indexes were calculated using these data. Same blood tests were performed after 8 hours of night fasting using the same methods in all participants of the control group.

Statistical analyses

Statistical analyses were performed by using SPSS 11.0.1 (April 2002; IBM Corp.; NY, USA). Assumption of normal (Gaussian) distribution was tested by one-sample Kolmogorov-Smirnov test. Variables were compared by gallstone disease status using a t-test (independent samples t-test and Mann-Whitney U tests) for continuous variables or a χ^2 test for categorical variables. Binary logistic regression analyses were used to determine parameters that had a significant effect on GBS disease.

RESULTS

Baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of the study population

	N	Minimum	Maximum	Mean	Std. Deviation
Age	253	8.00	94.00	55.7510	16.65182
Time on HD (months)	104	1.00	252.00	47.7885	46.09418
SI (mcg/dL)	104	6.00	200.00	75.1567	42.77336
SIBC (mcg/dL)	104	40.00	496.00	234.9231	71.80336
Ferritin (ng/mL)	107	.00	1500.00	825.7904	450.18036
CA (mg/dL)	105	5.30	13.10	9.0143	1.03380
P (mg/dL)	105	1.50	8.60	4.4905	1.41737
Total bilirubin (mg/dL)	105	.19	5.90	.7025	.57568
Direct bilirubin (mg/dL)	105	.10	4.52	.2632	.44052
ALT (U/L)	108	6.00	77.00	17.8796	11.39414
GGT(U/L)	108	7.00	472.00	38.9444	66.63919
Uric Acid (mg/dL)	106	3.90	9.30	6.1942	1.19535
ALP (U/L)	106	4.00	213.00	75.9717	34.30131
TG (mg/dL)	105	57.00	571.00	200.8190	108.80291
Total cholesterol (mg/dL)	105	60.00	359.00	171.4476	44.64152
LDL - cholesterol (mg/dL)	105	35.00	215.00	97.9810	33.35300
CRP (mg/dL)	106	.50	147.00	12.4585	21.25795
PTH (pg/mL)	104	4.00	1430.00	272.2162	312.02926
Hepatosteatosis	106	.00	1.00	.0283	.16662
BMI (kg/m^2)	106	13.00	36.80	24.0252	4.01352

HD: hemodialysis; SI: serum iron; SIBC: serum iron binding capacity; CA: calcium; P: phosphorus; ALT: alanine transaminase; GGT: gamma glutamyl transpeptidase; ALP: alkaline phosphatase; TG: triglyceride; LDL: low-density lipoprotein; CRP: c-reactive protein; PTH: parathyroid hormone; BMI: body mass index

In the present study, the prevalence of gallbladder stone (GBS) in hemodialysis patients was 34.6% (36/104), significantly higher than that of the control group: 12.9% (17/149; p=0.0001). In all study participants (HD patients and control group), patients with GBS were older than patients with no GBS (63.2±14.2 vs 53.7±16.7; p=0.0001). However, in hemodialysis patients, mean age was similar in patients with GBS and no GBS (64.3±13.8 vs. 60.1±16.6; p>0.05). Gender, number of childbirths, frequency of diabetes, proportion of patients on oral contraceptive medications, and existence of nephrolithiasis or hepatosteatosis were not different between patients with GBS and no GBS in all groups and in hemodialysis patients (chi-square p>0.05). Patients with GBS had a higher prevalence of units of blood transfusions than patients with no GBS in hemodialysis patients (2.0±2.9 vs. 0.9±1.3; p=0.047) (Figure 1).

Time on dialysis, body mass index, calcium, phosphorus, parathyroid hormone, uric acid, ALT, AST, GGT, and lipid parameters (LDL-C, HDL-C, total cholesterol, triglyceride, VLDL-C) were not different between patients with GBS and no GBS in hemodialysis patients (p>0.05).

Logistic regression analysis showed that the number of blood transfusions in the last year had the most significant effect, but LDL-C and ALP levels also had significant increasing effects on GBS in HD patients (Table 2).

DISCUSSION

In the present case-control study, we detected a 34.6% prevalence of gallbladder stones (GBS) in our hemodialysis patients. It was three times higher than detected in healthy controls (17/149: 12%). Previous studies in dialysis patients showed a wide range of prevalence of GBS between 3.85%-33.3% (4,5). To our knowledge, our study detected the highest prevalence of GBS disease in HD patients reported in the literature. Previously, the highest prevalence of GBS (33.3%) was reported from a study performed in a Sicilian population of hemodialysis patients (5). Its patient population was similar to our population in some respects, such as Sicilians and Turkish people are both Mediterranean and their diets are similar; mean age was 62.5, like us (62 in HD patient group), and both HD groups were including diabetics. On the other side, they had found a positive correlation between GBS prevalence and presence of diabetes, age, and high serum phosphorus levels. We found that prevalence of GBS was positively correlated with number of blood transfusions, alkaline phosphatase, and LDL-cholesterol levels in the hemodialysis population. Prevalence of GBS was positively correlated with age in all study groups but not in

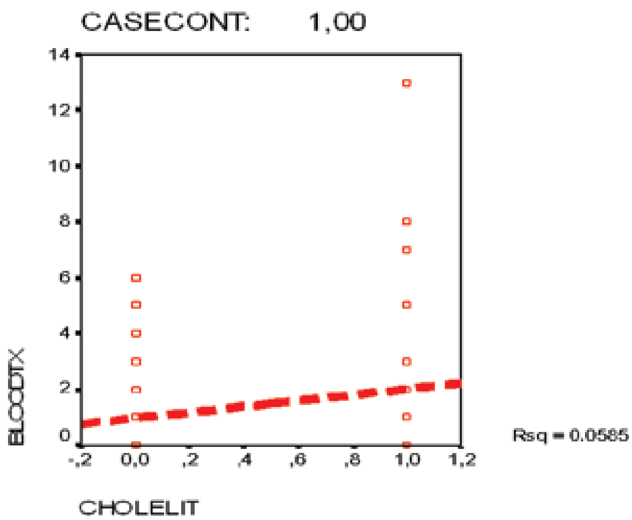

Figure 1. The frequency of blood transfusions in hemodialysis patients with and without gallstones (1: patients having gallstone disease, O: patients with no gallstone disease)

hemodialysis patients. Possibly, the prevalence of GBS in Mediterranean populations could be increased by multiple factors, such as type of diet. Although diet may have a role on the development of gallstones, it can not explain the difference between HD patients and non-uremic controls, because both are Mediterranean and consume nearly the same type of diet. In our study population of HD patients, the major factor increasing GBS was the number of blood transfusions. This might be caused by erythropoietin (EPO) resistance. In our HD patients, we did not evaluate the patients in respect of the type of the gallstone disease. Although we did not find any correlation between GBS disease and bilirubin levels, we could not exclude the hemolysis, at least in some of the patients. On the other side, solely the number of blood transfusions (2.0±2.9/year) in our HD patients is not enough to explain this high prevalence of GBS.

One study revealed a positive correlation between body mass index, parity, and biliary lithiasis in HD patients (11). Another small study on 11 regular HD patients showed increased bile cholesterol and increased saturation index, a decrease in primary, and an increase in secondary bile acids in the bile, which mimics the change in the spectrum of bile characteristics for cholecystolithiasis (8). There is no detailed information about the types of GBS in HD patients. However, one study reported that five out of seven GBS had been cholesterol-rich stones, and two out of seven had been mixed (cholesterol and bilirubin) stones in patients with chronic kidney disease (4). During a prospective study on 179 patients who underwent cholecystectomy for gallstone disease, a 69-year-old female with predialysis chronic kidney disease (CKD) was reported to have a black pigment gallstone with an irregular surface (12). X-ray diffractometry of this stone revealed a great amount of

Table 2. Logistic regression analysis: effects of variables on gallbladder stone in hemodialysis patients

	B	S.E.	Wald	df	Sig.	Exp(B)
Age	.038	.022	3.045	1	.081	1.039
Duration of HD (months)	.013	.007	3.638	1	.056	1.013
Blood transfusion (n)	.435	.163	7.116	1	.008	1.544
Ferritin (ng/mL)	-.001	.001	2.118	1	.146	.999
CA (mg/dL)	.067	.299	.051	1	.822	1.070
P (mg/dL)	-.375	.259	2.104	1	.147	.687
Total bilirubin (mg/dL)	-.218	1.135	.037	1	.848	.804
Direct bilirubin (mg/dL)	-.460	2.252	.042	1	.838	.631
ALT (U/L)	.049	.028	3.182	1	.074	1.051
GGT (U/L)	-.004	.009	.162	1	.688	.996
UA (mg/dL)	-.194	.245	.627	1	.429	.824
ALP (U/L)	.018	.009	4.189	1	.041	1.019
TG (mg/dL)	.003	.003	.823	1	.364	1.003
Total Cholesterol (mg/dL)	-.017	.010	3.087	1	.079	.983
LDL Cholesterol (mg/dL)	.024	.012	3.968	1	.046	1.025
CRP (mg/dL)	.021	.012	3.079	1	.079	1.022
PTH (pg/mL)	-.001	.001	.317	1	.573	.999
BMI (kg/m^2)	.017	.071	.056	1	.813	1.017
Constant	-3.897	4.504	.749	1	.387	.020

HD: hemodialysis; SI: serum iron; SIBC: serum iron binding capacity; CA: calcium; P: phosphorus; ALT: alanine transaminase; GGT: gamma glutamyl transpeptidase; UA: uric acid; ALP: alkaline phosphatase; TG: triglyceride; LDL: low-density lipoprotein; CRP: c-reactive protein; PTH: parathyroid hormone; BMI: body mass index

(50-60%) Whitlock tide ($(CaMg)^3$ $(PO^4)^2$), with the remaining 40-50% being calcium bilirubinate. The authors suggested that secondary hyperparathyroidism in patients with CRF and as a result of increased Ca x P product leads to increased excretion of Ca and P into bile and crystallization. One study in peritoneal dialysis patients showed that the prevalence of female gender, parathyroid hormone (PTH) levels, and serum creatinine levels was increased in patients having GBS, too (9). However, other studies did not confirm these results and could not find a correlation between PTH levels and GBS (2-5,8). In the present study, we could not find a relationship between PTH levels, Ca, P, and Ca x P product and GBS either.

Autonomic neuropathy is an important problem in long-term HD patients. One study revealed the falls of BP in 73%, itching of skin in 42%, constipation or diarrhea in 33%, filling of stomach in 25%, and decreased sweating in 17% of the long-term HD patients. Altogether, 85.9% of patients reported one or more subjective symptoms of neuropathy (14). The effect of autonomic neuropathy on gallbladder functions is not well known. Only one small study on CKD (including 19 HD patients) revealed no alteration in gallbladder functions (15). In the present study, we did not evaluate gallbladder functions. Therefore, gallbladder dysmotility due to uremic autonomic neuropathy could be responsible for the increased GBS prevalence in HD patients.

Limitations of our study were as follows: we did not study all hemolysis markers, such as lactate dehydrogenase, haptoglobin, and reticulocyte count; second, we did not determine the types of gallbladder stones (bilirubin, cholesterol, or mixed), which may be related to hemolysis or blood transfusions, and we had no information about gallbladder motility. The present study was designed as a case control study, and our primary aim was to detect the prevalence of GBS in HD patients and compare it with normal populations. Therefore, we did not evaluate the patients and control group in respect of GBS types. However, the present results demonstrated that the number of blood transfusions had a positive correlation with GBS prevalence. It seems reasonable to investigate hemolysis markers (LDH, haptoglobin, reticulocyte count), especially in hemodialysis patients who need blood transfusions due to EPO resistance. On the other side, gallbladder dysmotility may increase the tendency toward GBS formation in HD patients. Further controlled studies, including hemolytic markers and gallbladder functions, are needed to evaluate GBS in HD patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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