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Gallbladder Pathologies in Kidney Transplant Recipients: Single-Center Experience and a Review of the Literature

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Background: In patients with end-stage renal disease, cholelithiasis is observed with an increased frequency. In transplant recipients, symptoms might be obscured, which may delay the diagnosis and lead to complications. The aim of our study was to evaluate the frequency of gallbladder pathologies in kidney transplant recipients (KTRs) in the Caucasian population, and to discuss the potential benefits of prophylactic cholecystectomy before kidney transplantation (KT).





Material/Methods: Data from 434 patients who underwent KT was analyzed. Demographic data along with gallbladder status were collected from the pre-transplantation charts. We compared our results to data from the general Polish population.

Results: In our analyzed group of KTRs, there were 284 men and 150 women. Complete data, including abdominal ultrasound description, were available in 412 cases. In this group, 36 patients (8.74%) underwent cholecystectomy before KT. Other gallbladder pathologies (gallstones and polyps) were found in 41 patients (9.95%) at pre-transplantation evaluation. The incidence of gallbladder pathologies in KTRs, being mostly cholelithiasis, was higher than in the general Polish population.

Conclusions: In specific age subgroups of KTRs, the frequency of gallbladder pathologies was higher than in the general population. Prophylactic cholecystectomy may potentially offer benefits in these subgroups of patients.

MeSH Keywords: **Cholecystectomy • Cholelithiasis • Kidney Transplantation**

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Background

Cholelithiasis is one of the most common gastroenterological diseases with a frequency of 10–15% in the general population [1,2]. The indications for cholecystectomy are symptomatic gallbladder stones; however, in diseases such as diabetes and sickle cell disease, and in patients undergoing solid organ transplantation, prophylactic removal of the gallbladder is nowadays considered [1,2]. The treatment of choice is laparoscopic cholecystectomy. It has been proven that in patients with end-stage chronic kidney disease (CKD) on hemodialysis or after kidney transplantation (KTx), the frequency of cholelithiasis increases [3–6]. Moreover, patients after KTx receiving immunosuppression due to delayed diagnosis resulting from obscured symptomatology of inflammatory diseases and patients with decreased immune response may be at higher risk of complications of cholecystitis [7,8].

The aim of our study was to evaluate the frequency of gallbladder pathologies in kidney transplant recipients (KTRs) in a Polish university transplant center, and to discuss potential benefits of prophylactic cholecystectomy before KTx.

Material and Methods

We retrospectively analyzed data of 434 patients who underwent KTx in our center between January 2012 and December 2015. Demographic data were collected (age, gender, body mass index (BMI), history of dialysis) from pre-transplantation charts. To identify gallbladder pathologies, medical records of the patients were also reviewed. History of cholecystectomy before KTx, presumably for cholelithiasis based on medical history, and other data on gallbladder pathologies (e.g., stones, polyps) were collected from abdominal ultrasound descriptions (routinely performed prior to KTx).

Statistical analysis

Statistical comparisons were performed against data for the general Polish population published by Tomecki et al. [9]. Chi-squared tests were used with statistical significance considered for $P < 0.05$.

Results

There were 284 men and 150 women aged 50.21 ± 13.41 years (range 18 to 76 years) in the study group. Mean BMI of the patients was 25.47 kg/m^2 . A complete dataset, including description of abdominal ultrasound, was available in 412 cases (271 men and 141 women) (94.93%). In total, 77 patients (18.69%: men 16.97% and women 21.99%) had gallbladder pathology

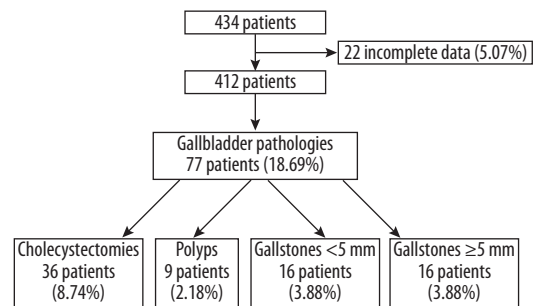


Figure 1. Gallbladder pathologies in the studies group.

upon qualification for transplantation and it was mostly cholelithiasis and polyps. Thirty-six patients (8.74%) underwent cholecystectomy before KTx. Gallbladder abnormalities were found in 41 patients (9.95%) in the pre-transplantation evaluation. There were 9 cases of gallbladder polyps (2.18%) and 32 cases of cholelithiasis (7.77%). Gallstones smaller than 5 mm in diameter were found in 16 patients and gallstones bigger or equal to 5 mm in diameter in 16 patients (Figure 1).

In the group of patients between the ages of 18 and 39 years, gallstones/polyps or medical history of cholecystectomy was found in 11% of patients (13.11% of men and 7.69% of women in that age range). In the group of patients between the ages of 40 and 60 years, gallstones or medical history of cholecystectomy was found in 17.16% (13.57% of men and 25% of women in that age range), and in patients older than 60 years, gallstones or medical history of cholecystectomy was found in 28.7% (27.14% in men and 31.58% in women in that age range) (Table 1).

Discussion

In the general population, gallstones have been estimated to be found in 10–15% of people. In Far East countries such as China, Japan, and Taiwan, cholelithiasis is found in 5–10% of women. Similar results can be found in reports from sub-Saharan countries, whereas in Caucasians in European countries such as Germany, Italy, Poland, the Czech Republic and Sweden, the frequency of gallstones is higher and is estimated to affect about 9–13% of men and 20–30% of women [2,6,10]. Only 1 report assessing the frequency of cholelithiasis in the general Polish population can be found in the literature. In that study cholelithiasis was diagnosed in 8.2% of men and 18% of women in the general population, and its incidence increased with age [9]. In our study, enrolling patients from one of the biggest Polish transplant centers, the incidence of gallbladder pathologies was 18.69% (16.97% in men and 21.99% in women) and was higher compared to the general Polish population from the

Table 1. Frequency of gallstones/polyps or medical history of cholecystectomy in kidney transplant patients depending on age range.

| Age | Men | Women | Total |
|-------|-----------------|-----------------|-----------------|
| 18–39 | 8/61 (13.11%) | 3/39 (7.69%) | 11/100 (11%) |
| 40–60 | 19/140 (13.57%) | 16/64 (25%) | 35/204 (17.16%) |
| >60 | 19/70 (27.14%) | 12/38 (31.58%) | 31/108 (28.7%) |
| Total | 46/271 (16.97%) | 31/141 (21.99%) | 77/412 (18.69%) |

aforementioned study. In the group of men aged 18–39 years, the incidence of cholelithiasis was significantly higher (13.11% vs. 4.24% for KTRs vs. general population, $P=0.001$). In women, the incidence was similar (7.69% vs. 7.6% for KTRs vs. general population, $P=0.989$). In the group aged 40–60 years the frequency was higher for men (13.57% vs. 8.74% for KTRs vs. general population, $P=0.688$) and for women (25% vs. 22.88% for KTRs vs. general population, $P=0.691$) but no statistical significance was demonstrated. A higher but also comparable rate of cholelithiasis in the general population as compared to our study patients was observed only in the group of women older than 60 years (38% vs. 31.58%, $P=0.579$). In males in our study aged older than 60 years, the frequency was 27.14%. Reference data for men in this age group was not available [9]. The incidence of gallbladder pathologies that we reported was a summation of gallbladder gallstones actually visualized on ultrasound examination as well as polyps and cholecystectomy in the medical history of patients. Polypoid lesions described in ultrasonography often show up as biliary sludge or cholesterol deposits in final pathology reports, therefore they were considered together with cholelithiasis [11].

There are many risk factors for gallstones including age, gender, race, obesity, diabetes, hyperlipidemia, oral contraceptive pills, pregnancy, rapid weight loss, CKD, hemodialysis, and the use of cyclosporine immunosuppression [2,12,13]. Lai et al. in an analysis of medical records of 4773 patients undergoing periodic health examinations in Taiwan concluded that the prevalence of gallbladder stones was significantly higher in patients with CKD than in those without it (13.1% vs. 4.9%, respectively; $P<0.001$) [3]. Kazama et al. noted that the prevalence of gallbladder stones in patients with CKD increased with the progression of disease stage, from 7.7% in CKD stage 1 to 21.3% in CKD stage 5 [14]. In another study in which the frequency of gallstones in hemodialysis patients was evaluated, increased percentage of cholelithiasis was observed in comparison to a control group (34.6% vs. 12%; $P=0.0001$) [4].

It has been proven that patients after KTx on cyclosporine immunosuppression have increased incidence of cholelithiasis. This is probably due to cholestasis and reduced bile flow caused by this drug [8,15–18]. In patients treated with tacrolimus based

immunosuppressive regimens, the incidence of cholelithiasis seems to be lower compared to cyclosporine; and it is not observed to be increased in patients treated with azathioprine and prednisone immunosuppression alone [15,19]. Therefore, the prevalence of cholelithiasis after KTx might differ depending on immunosuppression regimens.

Gallstone disease may lead to serious complications such as cholecystitis, acute mechanical jaundice, cholangitis, or biliary pancreatitis. The rate of serious symptoms or complications from gallstones has been estimated to be 1% to 2% annually [20]. The most common presentation of cholelithiasis is cholecystitis. In KTRs, the percentage of serious complications and morbidity and mortality because of the cholecystitis seems to be higher than in the general population, likely due to immunosuppression and its masking effect on the signs of inflammatory process [7,21]. Sarkio et al. [8] in their study of 1608 patients after KTx in Finland found that gallstones were present in 267 individuals. In this group, 102 patients (6.34%) had cholelithiasis diagnosed before KTx and 165 patients (10.25%) had cholelithiasis diagnosed after KTx during the median follow-up period of 7.4 years. In patients with cholecystectomy performed before KTx (72 patients), biliary complications (cholangitis) were observed in 1 case (1.39%), whereas in patients with gallstones diagnosed after KTx, biliary complications were found in 29 cases (14.8%). Among those complications, there were 21 cases of cholecystitis, 7 cases of choledocholithiasis, and 1 case of biliary pancreatitis. On the other hand, Jackson et al. [13] showed a small risk of complications in patients after KTx with gallbladder diseases. In their study of 411 patients, gallstones after KTx were present in 32 patients (7.79%) and other gallbladder abnormalities (gallbladder polyps, gallbladder wall thickening or contracted state, gallbladder sludge, and dilation of the common bile duct) in 35 patients (8.52%). In the studied group during the mean follow-up period of 4 years, no patient with cholelithiasis required cholecystectomy, and 2 patients with other gallbladder abnormalities required elective cholecystectomy with no complications.

It has been suggested that patients with gallstones smaller than 5 mm have a more than 4-fold increased risk of presenting with acute biliary pancreatitis [22], and in our study, half of the patients with cholelithiasis had gallstones smaller than 5 mm.

Table 2. Frequency of cholelithiasis and cholecystectomies in kidney transplant patients.

| Authors | Year | No of patients | Mean follow-up | Cholelithiasis | Biliary complications | Cholecystectomies | Complications after surgery | Recommended prophylactic cholecystectomy |
|--------------------------|------|----------------|----------------|----------------|-----------------------|-------------------|-----------------------------|--|
| Sutariya et al. [7] | 2014 | 350 | 2.48 years | – | 9 | 20 | 1* | Yes |
| Ru Da Lee et al. [23] | 2014 | 66 | 77.1 months | 11 | 2 | 0 | 0 | Yes |
| Sarkio et al. [8] | 2007 | 1608 | 7.4 years | 196 | 30 | 103*** | 4** | Yes |
| van Petersen et al. [16] | 2007 | 58 | 7.7 years | 12 | – | – | – | Yes |
| Jackson et al. [13] | 2005 | 411 | 4 years | 20 | 0 | 2 | 0 | No |
| Melvin et al. [24] | 1998 | 662 | 55.9 months | – | 12 | 52 | 6 | No |
| Lowell et al. [25] | 1993 | 87 | 13 months | 16 | – | – | – | Yes |

* Wound infection; ** one death and three biliary peritonitis; *** 17 urgent.

In the current literature there is a limited number of publications evaluating the frequency of cholelithiasis and its complications in patients after KTx. In a review of the literature from the last 20 years, there are only 7 studies on this topic (Table 2). The conclusions about prophylactic cholecystectomy in patients who qualified for KTx are contradictory, however, as most of them seem to promote this concept.

This study is one of the biggest cohort studies published so far regarding the problem of gallbladder pathologies in KTRs. Nevertheless, there were some limitations. It was a retrospective, single-center study and the ultrasound examinations were not standardized and were not directed to gallbladder pathologies. This may have resulted in an underestimation of the number of gallbladder pathologies. Another limitation was the lack of a longer than 4-year follow-up period for KTRs with gallbladder pathologies and an investigation related to potential long-term complications.

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Conclusions

In summary, we would like to emphasize that in KTx recipients the frequency of cholelithiasis is higher than in the general Polish population. A review of the literature showed that most authors promoted the concept of prophylactic cholecystectomy. In our opinion, prophylactic cholecystectomy for asymptomatic cholelithiasis may have potential benefits in patients who are qualified for KTx, however, more studies are needed to formulate a recommendation.

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Conflict of interest

None.

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