Complications of gallstone disease in kidney transplantation patients

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Abstract

Background. We studied the complications of gallstone disease in kidney transplantation patients and evaluated whether the screening and treatment of gallstones before acceptance to the kidney waiting list is relevant.

Methods. Complications of gallstone disease were evaluated in 1608 kidney transplantation patients on cyclosporine and long-term steroid treatment with median age 45.5 years, transplanted between 1990 and 2000. To evaluate the prevalence of cholecystolithiasis after kidney transplantation an abdominal ultrasound examination was cross-sectionally performed to a subgroup of 304 patients and the results were correlated to their serum lipid values, changes in BMI and use of statins.

Results. Pre-transplant cholecystectomy due to cholecystolithiasis (prerequisite for acceptance to kidney waiting list) had been performed on 71 (4%) of the patients. Thirty (15%) patients with diagnosed post-transplant gallstones and four without gallstones developed biliary complications. There were 25 cases of cholecystitis of which three resulted in gallbladder perforations. Seventeen patients (50%) with biliary complications required urgent surgery and one (3%) patient died of post-operative complications. In the subgroup of ultrasound examination patients (median 7 years post-transplant follow-up) 81% of the patients had no gallstones and 9% of the patients had gallstones had developed after transplantation. Seventeen patients (50%) with biliary complications required urgent surgery and one (3%) patient died of post-operative complications. In the subgroup of ultrasound examination patients (median 7 years post-transplant follow-up) 81% of the patients had no gallstones and 9% of the patients had gallstones had developed after transplantation. Patients with pre-transplant gallstones were older ($P < 0.01$) and patients with post-transplant gallstones gained the most weight during the follow-up. No differences in lipid values were found.

Conclusion. In transplantation patients, the complications of gallstone disease may be severe. Screening and treatment of pre- and post-transplantation gallstone disease are recommended.

Keywords: complication; gallstone disease; kidney transplantation

Introduction

Gallstone disease is very common in the western population. Over 10% of the people in western countries have gallstones [1,2]. In Finland, the prevalence has been the same as in other western countries [3]. The incidence rises with age and it is higher in women. Complications of untreated gallstone disease such as cholecystitis, cholangitis or biliary pancreatitis occur in 1% of the population annually [4]. The main risk factors for gallstone disease are high age, female gender and obesity. Also, diabetic patients seem to be at higher risk of developing gallstone disease. Smaller risk factors for gallstone disease are childbearing and some medications [1].

Immunosuppressive medication predisposes transplantation patients to the formation of gallstones [5]. Because of such therapy, the complications of gallstone disease can be severe in this patient group and the diagnosis can be delayed [6].

In the general population, and currently also in diabetic patients, only symptomatic gallstone disease is considered as an indication for cholecystectomy. In the organ transplantation population there is some controversy whether asymptomatic gallstone disease should also be screened and treated before transplantation, although according to European guidelines pre-transplant cholecystectomy might be considered in cases of cholelithiasis [7]. In Finland abdominal screening with ultrasound and cholecystectomy in cases of gallstones has been required before acceptance to the kidney waiting list.

The aim of this study was to examine the occurrence of gallstones after kidney transplantation and the complications thereof. After acquiring this information we wanted to re-evaluate our policy concerning the treatment of gallstone disease before kidney transplantation.
Subjects and methods

All kidney transplants in Finland are performed at one centre. The follow-up of the patients is performed by local nephrologists, who regularly send their reports to the Finnish Kidney Transplantation Registry. Helsinki University Hospital’s Nephrological Unit organizes the follow-up of the patients from the Helsinki area.

Complications of gallstone disease were evaluated in the cohort of adult patients who underwent kidney transplantation between 1990–2000 at Helsinki University Hospital. During that period, 1698 kidney transplants were performed on 1608 adult patients (977, 61% men). During the study period, 86 patients received two and two patients received three kidney grafts. Thirty-nine of the kidney transplants were from living donors.

The median age of the patients at the time of transplantation was 45.5 years (range 16.1–76.3 years). Before the transplantation, 907 (56%) patients were on haemodialysis and 701 (44%) were on peritoneal dialysis (CAPD). Polycystic kidney disease was the cause of uraemia in 247 (15%) of the patients, glomerulonephritis in 478 (28%), other kidney disease in 335 (23%), diabetes mellitus in 415 (26%) and other systemic disease in 133 (8%) of the patients. The median age of patients with polycystic kidney disease was 53.6 years, 45.6 years in patients with other kidney disease, 40.5 years in patients with diabetes mellitus and 48.8 years in patients with other systemic disease. During the time period following transplantation 276 (17%) of the patients had died.

In general, the immunosuppressive medication consisted of cyclosporine, azathioprine and permanent steroid therapy. Tacrolimus was used in 4% of the transplantations. Rejections were treated with high-dose methylprednisolone for 5 days and if this treatment failed, with monoclonal antibody OKT3 or plasmapheresis. Ranitidine 150 mg or omeprazole 20 mg was used during at least the first post-transplantation month as ulcer prophylaxis and acetylsalicylic acid (ASA) 50–100 mg as thrombosis prophylaxis.

Clinical data of patients accepted to the kidney waiting list, data of the post-transplantation period at the hospital and follow-up data sent regularly by the local nephrologists were gathered from the original patient records and from the Finnish Kidney Transplantation Registry. Information about the patients’ history of gallstone disease, i.e. diagnosed gallstone disease or cholecystectomy before transplantation was registered. A complementary questionnaire about diagnosed post-transplantation gallstone disease and possible cholecystectomies was sent to those 783 patients for whom that data was insufficient. Replies were received from 470 (60%) of these patients. At the end, unambiguous data on the patients having post-transplant gallstone disease could be found on 940 (58%) of the 1608 kidney transplantation patients. In the remaining 668 patients, data on gallbladder examinations was not available.

To evaluate the prevalence of both asymptomatic and symptomatic choledocholithiasis after kidney transplantation, from the 451 kidney transplantation patients from Helsinki area an abdominal ultrasound (US) was performed during the years 2003–2004 on the 304 patients still having a functioning graft and remaining in the follow-up at the Department of Nephrology, Helsinki University Hospital. In addition, data on serum lipid values (total serum cholesterol, serum HDL and serum triglycerides), body mass index (BMI) and the use of statin medication at the time of transplantation and at the end of the follow-up, were collected from the patient hospital records.

Ethics: The study protocol was approved by the Ethics Committee of Helsinki University Hospital. The patients gave their informed consent.

Statistics: The variables were compared using student’s t-test and chi-squared test. The data were expressed as median and range or mean and 95% confidence intervals. Significance was established at \( P < 0.05 \).

Results

The median follow-up time after transplantation was 7.4 years. Cholecystectomy had been performed on 71 (4%) patients before acceptance to the kidney transplantation waiting list. After the transplantation, 196 patients (56% men) were diagnosed as having gallstones—in 165 patients (84%, 56% men) the gallstones had developed after the transplantation (Figure 1). Gallstone disease was found in 12% of patients with polycystic kidney disease, 11% with glomerulonephritis, 16% with other kidney disease, 9% with diabetes and 21% with other systemic disease \( (P < 0.01) \). Gallstone disease was most uncommon in patients with diabetes, but diabetics were also slightly younger than other recipients (median age 40.5 vs 48.8 years at the time of transplantation).

Biliary complications after transplantation

After kidney transplantation, 30 patients (15%, 70% men) with present or previous gallstones developed a biliary complication and also four of the patients without gallstones (Figure 1, Table 1). There were 25 cases of cholecystitis including all of the four patients without gallstones. Seven patients with post-transplant gallstones were found to have choledocholithiasis and one patient who had undergone pre-transplant cholecystectomy had post-transplant cholangitis, although no gallstones were found. One patient with post-transplant gallstones had biliary pancreatitis. One male patient who was operated on because of cholecystitis died of post-operative complications 3 months later. Three non-fatal gallbladder perforations, one without gallstones, with biliary peritonitis were found. Seventeen of the patients with biliary complications required urgent surgery. Two of these patients had cholecystitis without gallstones. One patient with cholecystectomy before kidney transplantation was diagnosed with cholangitis after the transplantation. The post-transplantation biliary complications of the 196 patients with diagnosed gallstones are presented in Table 1.

The mean duration of dialysis treatment was 660 days (95% confidence interval 576.9–742.5 days) in patients with post-transplant gallstones compared to 539 days (95% confidence interval 509.5–568.5 days) in patients without gallstones \( (P < 0.05) \).
There were no differences between the patients with (median 365 days) or without gallstones (median 366 days) in the time spent on the kidney waiting list. The occurrence of gallstone complications had no relation to the time spent in dialysis treatment.

Rejection treatments were observed in 23% of both the patients with post-transplant gallstones and the patients with pre-transplant gallstones or no gallstones. Nor were there differences in rejection treatments in patients with gallstone complications or no complications (27% vs 20%).

**Development of cholelithiasis after transplantation**

In order to find out the risk of developing gallstones after the transplantation, ultrasound screening of a subgroup of 304 (176, 58% men) kidney transplantation patients was performed (Table 2). The median interval between transplantation and ultrasound examination was 7 years. In this group, 245 (81%) had no gallstones visible on the ultrasound, 31 (10%) patients had gallstones and in 28 (9%) no gallbladder could be seen in the ultrasound, i.e. they had a history of cholecystectomy. According to the patients’ records in 12 (39%) of the 31 patients with gallstones or cholecystectomy, gallstones had retrospectively revealed to have been diagnosed already at the time of kidney transplantation, i.e. during the waiting time for kidney transplantation. Gallstones developed in 28 (10%) patients after transplantation. Four patients (one with gallstones diagnosed after transplantation) developed a biliary complication (three cholecystitis, one choledocholithiasis) during the follow-up. None of these complications were fatal.

Patients with pre-transplant gallstones were significantly older than patients without gallstones (52.3 vs 44.2 years, P < 0.01). Patients with post-transplant gallstones had gained more weight during the follow-up. The change in BMI was +2.0 in this group compared to +1.1 in patients without gallstones and +0.9 in patients with a history of pre-transplant gallstones/cholecystectomy (N.S.). Comparison of lipid profiles before and after kidney transplantation is presented in Table 2. All but one of the patients with gallstones developed after the transplantation had cyclosporine as the main immunosuppressive medication.

**Discussion**

In the present series consisting of 1608 kidney transplantation patients with a median age of 36 years, we observed the development of gallstones in 165 (10%) patients after transplantation. The incidence of gallstones after transplantation was significantly lower than in the general population (27% vs 20%). The low incidence of gallstones after transplantation is likely due to the use of cyclosporine as the main immunosuppressive medication. Cyclosporine is known to increase the risk of gallstones, but the overall incidence of gallstones after transplantation is lower than in the general population. This may be due to the selective nature of kidney transplantation patients, who are typically younger and healthier than the general population.

**Table 1.** Biliary complications in 196 patients with gallstones after kidney transplantation

<table>
<thead>
<tr>
<th>Gallstones diagnosed before transplantation</th>
<th>Gallstones diagnosed after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystitis</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>perforation</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>0</td>
</tr>
<tr>
<td>Biliary pancreatitis</td>
<td>0</td>
</tr>
<tr>
<td>Cholecystectomies</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>for biliary complications</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

**Fig. 1.** Distribution of diagnosed gallstones, cholecystectomies and biliary complications in 1608 kidney transplantation patients.
At the time of transplantation

After the follow-up

Kidney transplantation and gallstone disease

7 years follow-up time after transplantation. This is

Plantation developed gallstones during a median

Patients without gallstones
d = 245

Patients with
gallstones diagnosed
before the transplantation

Gallstones diagnosed after
the transplantation
d = 28

<table>
<thead>
<tr>
<th>Age (median, range)</th>
<th>44.2 (16.1–69.4)</th>
<th>52.3 (30.2–70.0)</th>
<th>45.9 (25.5–60.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>143/102</td>
<td>14/17</td>
<td>19/9</td>
</tr>
<tr>
<td>BMI (median, range)</td>
<td>23.1 (16.3–30.7)</td>
<td>24.7 (15.8–30.5)</td>
<td>23.5 (17.3–29.7)</td>
</tr>
<tr>
<td>Cholesterol (median, range)</td>
<td>5.5 (3.1–10.7)</td>
<td>5.4 (4.1–9.0)</td>
<td>5.4 (3.4–7.9)</td>
</tr>
<tr>
<td>HDL (median, range)</td>
<td>1.2 (0.2–6.8)</td>
<td>1.3 (0.6–2.3)</td>
<td>1.2 (0.6–1.7)</td>
</tr>
<tr>
<td>Triglyceride (median, range)</td>
<td>1.9 (0.4–9.0)</td>
<td>1.7 (0.6–3.0)</td>
<td>1.7 (0.7–3.6)</td>
</tr>
<tr>
<td>Follow-up time in years (median, range)</td>
<td>6.8 (1.0–14.4)</td>
<td>6.5 (0.4–13.6)</td>
<td>8.1 (1.4–13.2)</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>51.9 (24.3–78.4)</td>
<td>58.3 (39.1–74.3)</td>
<td>54.6 (31.4–68.3)</td>
</tr>
<tr>
<td>BMI (median, range)</td>
<td>24.2 (14.7–39.9)</td>
<td>25.6 (14.4–40.7)</td>
<td>25.5 (17.9–37.2)</td>
</tr>
<tr>
<td>Cholesterol (median, range)</td>
<td>4.9 (2.8–8.9)</td>
<td>4.9 (3.0–6.6)</td>
<td>4.8 (3.5–7.1)</td>
</tr>
<tr>
<td>HDL (median, range)</td>
<td>1.5 (0.7–5.6)</td>
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<td>1.7 (0.9–3.1)</td>
</tr>
<tr>
<td>Triglyceride (median, range)</td>
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<td>1.5 (0.8–3.0)</td>
<td>1.3 (0.6–3.4)</td>
</tr>
<tr>
<td>Statin started during the follow-up (%)</td>
<td>110 (45)</td>
<td>13 (42)</td>
<td>16 (57)</td>
</tr>
</tbody>
</table>

\(^a\)Includes patients who have undergone cholecystectomy before transplantation.

\(^b\)P < 0.01 in patients without gallstones vs patients with gallstones diagnosed before the transplantation.

45.5 years, 6.3% of the patients (5% of the males and 9% of the females) were diagnosed to have gallstone disease before the transplantation. After a follow-up of a median of 7 years, 267 (17%) patients were diagnosed with gallstones (15% of males and 21% of females), 62% of them developed after transplantation. To evaluate the exact prevalence of both asymptomatic and symptomatic gallstones, an ultrasound examination was performed on all 304 Helsinki area patients with functioning kidney graft. In this subpopulation, the prevalence of gallstone disease was 19%. In a general population under 50 years of age, the prevalence of gallstone disease is 5–15% in women and 4–10% in men and in a population over 50 years of age the percentages are 25% and 10–15% [1]. In a Finnish autopsy study from the 1980s, age-adjusted rates for gallstone disease were 15.9% in women and 8.7% in men [3]. The prevalence of gallstone disease in solid organ transplantation candidates does not significantly differ from that of the general population. In Greenstein et al.’s [8] report on 211 kidney transplant recipients, the prevalence of gallstones was 7%. In a Turkish material of kidney transplantation candidates, gallstones were found in pre-transplant screening in 9.7% of the patients (male/female ratio 11/10) [9]. In a recent review article, the aggregate pre- and post-transplant prevalence of gallstone disease was 16% in pancreas and kidney transplantation patients [10]. Our results are in accordance with these studies. Despite the male predominance in kidney transplantation patients and female predominance of gallstone disease in the general population, the high incidence of gallstone disease in kidney transplanted males is noticeable.

In the present series, 10% of kidney transplantation patients without gallstones at the moment of transplantation developed gallstones during a median 7 years follow-up time after transplantation. This is in agreement with Kao et al.’s [10] review article where the aggregate prevalence of post-transplantation gallstones was 12% in kidney and pancreas transplantation patients. Cyclosporine use has been associated with the formation of gallstones probably due to cholestasis and reduced bile flow [11]. In this study, practically all patients who developed gallstones after transplantation had cyclosporine as the main immunosuppressive medication.

The aetiology of gallstones is multifactorial with predisposing factors of age, obesity, sex and diabetes [1]. In this study, the patients with pre-transplantation gallstones were significantly older than patients without gallstone disease. The patients who developed gallstones after transplantation had gained the most weight during the follow-up, although the difference was not significant. No differences could be seen in lipid values. There were fewer diabetics and more patients with other systemic disease in patients with gallstone disease compared to patients without gallstones. On the other hand, patients with diabetes were younger than other kidney transplantation patients.

In the general population, the rate of serious complications of gallstone disease is 1–2% per year [12]. In the present series, 34 biliary complications, 2% of all the patients, one of them fatal, were recorded during the follow-up. This includes three cases of biliary peritonitis. Four cases of cholecystitis (one perforated) occurred in patients without gallstones. Two of the patients with acalculous cholecystitis and 15 (8%) of the patients with gallstone disease needed emergency operations. In total, 29% of transplantation patients with diagnosed gallstones had undergone cholecystectomy during the follow-up. The risk of gallstone complications in transplantation patients seems to be higher and the progression of symptoms...
seems to be more rapid [10]. Because of immunosuppressive therapy, the complications of gallstone disease can be more severe and the diagnosis delayed in transplantation patients. In two studies from the 1990s, the incidence and morbidity of symptomatic gallstones after kidney transplantation was low [8,13]. In another study, surgical morbidity occurred in 14%, mortality was 7% and the kidney grafts were lost in 20% of the patients with symptomatic gallstones operated after transplantation and in the same report, in a series of 45 patients with cholecystectomy performed prior to kidney or pancreas transplantation, there was neither morbidity nor mortality [6].

In the Finnish Transplantation Unit, cholecystectomy in cases of gallstones has been prerequisite for acceptance to the kidney waiting list. Few patients have developed gallstones during the kidney waiting time or slipped through the screening with gallstones. In this study, two patients with gallstones had gallbladder perforations and one patient died of post-operative complications of cholecystitis with gallstones after kidney transplantation. The complication rate of gallstone disease was 15%, which we consider high. We maintain our policy to recommend screening and surgical treatment also of symptomless gallstone disease before acceptance to the kidney transplantation waiting list. We also consider adding screening for gallstone disease to the routine post-transplantation follow-up program to find the patients before the complications occur.

In conclusion, the incidence of gallstone disease in the uraemic patients accepted to the kidney transplantation waiting list does not differ from that of the normal population. The complications of gallstone disease can be severe in transplantation patients. Screening and treatment of pre- and post-transplantation gallstone disease are recommended. However, additional studies are needed to evaluate the morbidity of cholecystectomy in this patient group.

Conflict of interest statement. None declared.

References

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