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The individualization of immunosuppressive therapy in a kidney transplant recipient after gastric bypass surgery — a case report

Abstract

Obesity is one of the most common relative contraindications to kidney transplantation (KTx), the optimal treatment method for end-stage kidney disease (ESKD). Weight reduction is recommended for patients with a body mass index (BMI) exceeding 35–40 kg/m^2 before transplantation, with bariatric surgery as a potential therapeutic option.

Both obesity and changes in gastrointestinal tract anatomy, absorption surface, enzyme secretion, and hormonal balance resulting from bariatric surgery may impact the pharmacokinetics and pharmacodynamics of drugs, including immunosuppressants. We present a case of a 40-year-old female with ESKD due to hypertension nephropathy, who underwent a Roux-en-Y gastric bypass procedure for weight reduction and had a history of partial bowel resection due to hernia incarceration before being qualified for KTx.

Following KTx, the patient's therapeutic drug monitoring consistently indicated subtherapeutic blood levels of tacrolimus (TAC). Despite dose adjustments and alterations in medication formulations, achieving and maintaining adequate TAC levels proved to be a challenge, eventually requiring the addition of fluconazole, a cytochrome P450 inhibitor.

In conclusion. For KTx recipients with a history of bariatric surgery, personalized and tailored treatment approaches are essential. This involves considering the appropriate scheme of immunosuppression, drug formulation, route of administration, and drug dosage guided by monitored therapy.

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Key words: kidney transplantation, bariatric surgery, obesity, tacrolimus

INTRODUCTION

Kidney transplantation (KTx) is the best method of renal replacement therapy. Patients eligible for transplantation must meet certain criteria, including the absence of comorbidities that are contraindications to transplantation [1, 2]. One of the relative contraindications to KTx is obesity, which is associated with worse short and long-term outcomes and an increased risk of complications in the transplant recipient. In the early post-transplant period there are mainly perioperative complications, including wound infection, dehiscence, incisional hernia, lymphocele, longer hospital stay and re-hospitalization, but there are also reports of a higher risk of delayed graft function (DGF) and acute rejection (AR) [3, 4]. Obesity-related comorbidities, such as hypertension, coronary artery disease, heart failure, obstructive sleep apnea, dyslipidemia and diabetes mellitus — both type-2 and new-onset diabetes mellitus, which obese individuals are two-times more likely to develop after KTx, greatly increase the risk of cardiovascular incidents, the leading cause of death in KTx population [5–8]. Obesity is also associated with worse long-term graft outcomes, particularly

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due to induced hyperfiltration and proteinuria leading to glomerular fibrosis, increased levels of pro-inflammatory cytokines, and also a higher risk of sub-therapeutic immunosuppression [4, 9]. Hence, in potential kidney recipients with obesity (BMI > 35 kg/m^2), weight reduction before transplantation is recommended. In patients in whom such reduction cannot be achieved by changing eating habits, increased physical activity, or pharmacotherapy, bariatric treatment should be advised [10].

One of the essential conditions for ensuring proper and long-lasting function of the transplanted kidney is the patient's use of adequate immunosuppressive treatment. The basic immunosuppressive treatment regimen after KTx includes glucocorticosteroids (GCS), calcineurin inhibitors (CINs): cyclosporine (CsA) or tacrolimus (TAC), and mycophenolic acid [11]. Calcineurin inhibitors, including TAC, are drugs with a narrow therapeutic window; their too-low blood concentration increases the risk of organ rejection, both acute and chronic, and consequently poor graft function. On the other hand, too high concentration increases the risk of side effects: acute and chronic nephrotoxicity, increased susceptibility to infections, development of neurological complications, hypertension, carbohydrate metabolism disorders, including diabetes, and the occurrence of cancer. Hence, it is necessary to monitor drug levels in the blood both early and late after transplantation. TAC, the most commonly used calcineurin inhibitor in the immunosuppression regimen after KTx is characterized by high pharmacokinetic and pharmacodynamic variability, which is reflected in the high inter- and intra-individual variability of its metabolism.

The pharmacokinetics of the drug is influenced by both genetic and a large number of clinical factors [12, 13]. When optimizing and personalizing TAC therapy, in addition to the recipient immune risk, various other factors must be taken into account, such as differences in the rate of TAC metabolism in individual patients, age, comorbidities, behavioral habits, and other medications taken [14]. One factor that also affects TAC metabolism is body weight, and it has been shown that patients with higher body weight require lower doses of the drug [15].

Little is known about the effects of bariatric surgery on the pharmacokinetics and pharmacodynamics of the drugs taken by patients after the surgery, including immunosuppressants. Available studies indicate that patients who have undergone bariatric surgery have an altered drug bioavailability compared to the non-bariatric population and may need to be re-dosed at much higher doses to achieve therapeutic drug concentrations [16].

CASE REPORT

A 40-year-old female patient with end-stage kidney disease (ESKD) probably in the course of long-term hypertensive nephropathy, on peritoneal dialysis (PD) for 2 years and then on hemodialysis (HD) for 5 years was qualified for KTx.

The patient had a history of poorly controlled hypertension for at least 8 years before starting dialysis. In 2010, during a hospitalization due to a hypertensive breakthrough, ESKD was diagnosed and the patient was qualified for PD. Two years later, due to gastrointestinal obstruction caused by hernia entrapment in the scar after Tenckhoff catheter implantation surgery, resection of a section of the small intestine was performed and the patient was converted from PD therapy to HD.

The patient also suffered from pathological obesity of the third degree (weight 100 kg with a height of 156 cm, BMI = 41.1 kg/m^2); weight reduction was recommended in preparation for KTx surgery. The patient's declared change in lifestyle and eating habits did not bring the expected results, so in April 2015, bariatric surgery — gastric exclusion with Roux-en-Y loop anastomosis (RYGB — Roux-en-Y gastric bypass) was performed. Within two years, the patient lost weight to 63 kg (BMI 26 kg/m^2). In 2016, as preparation for KTx, laparoscopic cholecystostomy was performed to remove gallstones.

At the end of 2016, the patient was placed on the National Transplant Waiting List and in October 2017 received a cadaveric kidney from a 35-year-old donor who died as a result of CNS hypoxia. The number of incompatible antigens (mismatch) in the HLA system was 3; the PRA (panel reactive antibodies) maximum was 6%, and the last before KTx was 0%. The cold ischemia time (CIT) was 30 hours, warm ischemia time (WIT) was 25 minutes.

Due to the long ischemic time and indirect immunological risk (young donor — young recipient), the patient was qualified according to current recommendations for a three-drug immunosuppression regimen with basiliximab induction [11]. The patient received GCS:

methylprednisolone infusions for the first 3 days (a total of 750 mg), followed by prednisone at a dose of 20 mg SID, TAC at a dose of 0.1 mg/kg BID (6 mg BID) and mycophenolate mofetil (MMF) at a dose of 1000 mg BID. The patient received the first dose of oral immunosuppressants 2 hours before surgery.

Due to the serological status of the CMV IgG-positive donor and IgG-negative recipient, the patient received valganciclovir as prophylaxis against the development of cytomegalovirus (CMV) disease. In addition, nystatin and trimethoprim with sulfamethoxazole in standard doses were used as prophylaxis. Due to the delayed graft function she required 3 HD sessions, the last one on the 11th day after surgery. Gradual improvement in blood flow was observed in next days, over several Doppler ultrasound examinations of the transplanted kidney.

On day 3 after KTx, the TAC C0 concentration (the minimum concentration before the next drug dose) was determined for the first time, which was 4.4 ng/mL. According to the recommendations, the expected concentrations in the first month after KTx should be in the range of 12–15 ng/ml [11]. Due to the non-therapeutic concentration of the drug, the daily dose of TAC was increased by 23% (by 3 mg a day) and more frequent checks of TAC concentrations were performed, to adjust the dose accordingly.

On day 6 after the procedure, the C0TAC concentration, despite the dose increase, remained subtherapeutic at 4.6 ng/mL; the dose was increased again by 25% (to 10 mg BID). On the 9th day after the procedure, the patient's then ingested form of TAC was converted to an extended-release form, taken according to the drug's specifications (SmPC) once daily at a dose of 20 mg.

On the 10th day after the procedure, the TAC concentration was even lower, at 3.0 ng/dL. The dose was increased to 20 mg BID (TAC extended-release form). In addition, in view of potential impaired absorption of MMF, the drug was converted to mycophenolate sodium (MPS: 360 mg every 6 hours). The concentration of mycophenolic acid was not determined, as there was no such possibility at the Center at the time.

On day 12, due to still subtherapeutic TAC concentrations (6.6 ng/dL), the dose was increased to 25 mg BID (still an extended-release formulation). In addition, fluconazole was added to the therapy to increase drug concentrations. Only this dosage, supplemented with a cytochrome P450 inhibitor, allowed a gradual achievement of higher concentrations, close to the recommended therapeutic levels for the given period after KTx — on the 16th and 19th postoperative days 9.3 ng/mL and 11.8 ng/mL, respectively. On the 21st day after KTx, the patient was discharged with improving graft function (serum creatinine level 3.4 mg/dL, eGFR 20.7 mL/min/1.73 m^2) and with the recommendation to take TAC (extended-release form) at a dose of 20 mg BID (total dose 40 mg per day), MPS 360 mg 4 times a day (total dose 1440 mg per day), prednisone 20 mg for further gradual dose reduction until reaching the target dose of 5 mg per day after 3 months. Other medications: fluconazole, trimethoprim with sulfamethoxazole, valgancyclovir, omeprazole, metoprolol, amlodipine, doxazosin, calcium carbonate, alfacalcidol, cyanocobalamin (once monthly).

Normalization of graft function (serum creatinine 0.87 mg/dL; eGFR 86 mL/min/1.73 m^2) was already observed in post-transplant outpatient clinic care at 43 days after KTx. Fluconazole was used until day 33 after KTx; no significant reduction in TAC was observed after the drug was discontinued.

As time passed after KTx, reduced need for TAC was observed; however, significant fluctuations in drug concentrations were still observed in the following weeks in outpatient care, so drug concentrations were closely monitored and the dose was modified (from 8 to 12 mg per day) according to current needs (on average every 2 weeks). After about a year of KTx, the patient reached a stable, desired therapeutic range of TAC, which was in the range of 5.0–8.0 ng/mL when taking extended-release TAC in a 6 mg BID regimen.

At present, the patient is 6 years post KTx, has good graft function, takes extended-release TAC 4 mg BID, MMF 500 mg 4 times a day, prednisone 5 mg (other medications: spironolactone, metoprolol, amlodipine, ramipril, alfacalcidol, vitamin B12). Moreover, she also maintains a stable body weight with a BMI of 30–32 kg/m^2.

DISCUSSION

Obesity is one of the risk factors for the development of chronic kidney disease, therefore obese patients are often qualified for kidney replacement therapy and are considered potential candidates for KTx. Patients with

a BMI > 30 kg/m2 are recommended to reduce weight before transplantation, and patients with a BMI > 35–40 kg/m^2 may benefit from bariatric surgery before transplantation [17].

Bariatric surgery can be divided into three main groups depending on the technique of the procedure [18]:

1. Restrictive — limiting the volume of food intake. This group includes, nowadays the most commonly performed, sleeve gastrectomy (LSG, laparoscopic sleeve gastrectomy) and an increasingly rarer procedure of placing an adjustable gastric band (LAGB, laparoscopic adjustable gastric banding).
2. Exclusionary: biliopancreatic diversion (BPD, biliopancreatic diversion) — involving excision of the distal part of the stomach and gastrointestinal anastomosis; most of the small intestine is excluded from the passage.
3. Restrictive exclusion: gastrointestinal bypass (Roux-Y-gastric bypass [RYGB], mini-gastric bypass [MGB]), biliopancreatic diversion with duodenal switch (BPD-DS, biliopancreatic diversion with duodenal switch), as well as new methods of metabolic surgery: duodenopancreatic exclusion with single anastomosis (SADI, single anastomosis duodeno-ileal bypass) or gastric-pancreatic exclusion with single anastomosis (SAGI, single anastomosis gastric-ileal bypass).

In Poland, LSG and RYGB procedures are most commonly performed [10].

The Roux-en-Y method is considered the "gold standard" of bariatric surgery. It involves cutting off a smaller part of the stomach and connecting it to the small intestine; the rest of the stomach (30–50 mL) with the duodenum forms an enzyme loop. The junction of the enzymatic and digestive loops is located about 100 cm from the gastric reservoir (leading to a reduction in nutrient absorption), and it is only at this point that the digestive contents mix with pancreatic enzymes and with bile, allowing for efficient digestion and absorption [19]. This operation leads to significant changes in the gastrointestinal hormonal balance.

The RYBG method is associated with more postoperative complications compared to LSG, which may be related to the difficulty of the operation, although it has better efficacy in controlling comorbidities such as diabetes mellitus, hypertension, and dyslipidemia, as well as better long-term outcomes in terms of weight control than LSG [20]. In the case described here, the patient underwent this type of operation.

Surgical alteration of the anatomical conditions of the gastrointestinal tract has pleiotropic effects on intestinal physiology, the endocrine system, mainly in terms of secretion of incretin hormones, neuronal stimulation, changes in bile acid metabolism, regulation of lipid metabolism, and alteration of the microbiome. Much attention is paid to changes in the secretion of hormones of the pancreatic-gastrointestinal axis [21]. Some bariatric methods [e.g., RYBG] involve the exclusion of the long gastrointestinal tract. This leads to a reduction in the length of the intestines, and consequently also changes the drug absorption surface. The passage time of the drug becomes insufficient for full absorption, which directly affects the pharmacokinetic and pharmacodynamic properties of drugs. In addition, with a decrease in gastric volume, there is also a decrease in hydrochloric acid secretion and an increase in gastric pH, leading to impaired dissolution and absorption of drugs that require an acidic environment for these processes. Absorption of lipophilic drugs (e.g., phenytoin, selective serotonin receptor inhibitors, and thyroxine) depends on the availability of bile acids; bypassing the duodenal portion of the intestine can lead to impaired dissolution and absorption [22]. On the other hand, some studies show increased drug absorption after bariatric surgery, which may be attributed to hypertrophy of the gastrointestinal mucosa that results in increased absorption in the residual portion of the intestine after surgery [23].

TAC is a highly lipophilic, poorly water-soluble drug which determines its low bioavailability and bioavailability – on average 25%, but with high individual variability (from 4 to 89%) [24]. Such low bioavailability is mainly determined by a first-pass effect controlled primarily by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 and the transport protein P-glycoprotein (P-gp), which show their expression in both the intestine and liver. TAC reaching the intestinal epithelial cells is metabolized by CYP3A5 and then ejected back into the intestinal lumen by P-gp [12]. The amount of CYP3A5 decreases from the proximal to distal part of the intestine, and the activity of the enzyme in the terminal small intestine and colon is low. P-gp activity seems to show an inverse relationship: it increases progressively from the stomach toward the large intestine. Hence, TAC may be more effi-

ciently absorbed from the distal than the proximal gastrointestinal tract [25]. On the other hand, MMF is absorbed mainly in the stomach and rapidly metabolized by plasma esterases to its active form. Therefore, by analogy, fearing that, like TAC, mycophenolic acid would not reach adequate blood concentration, in the patient described, the form of the drug with gastric absorption was changed to mycophenolate sodium, a form with intestinal absorption. The study, which described six patients undergoing bypass bariatric surgery, showed significantly lower levels of both TAC and mycophenolic acid compared to data from a population not undergoing such surgery [26].

In our recipient, target TAC concentration could not be achieved in the initial post-transplant period due to the bariatric surgery — "gastric bypass" — during which a 50 mL stomach was created and an enzyme-digestive loop was connected approximately 100 cm from the gastric reservoir, as well as due to previous resection of a part of the small intestine. It was necessary for her to use 0.77 mg/kg/day doses, many times higher than the commonly recommended 0.2 mg/kg/day, and the TAC formulation was also changed from twice daily to the extended-release formulation routinely recommended to be taken once daily. In the case described here, the drug was used at a dosage inconsistent with the SmPC, twice daily. It should be noted that the repeatedly increased doses of the drug were well tolerated by the patient; no adverse effects were observed, as the drug did not reach an adequate concentration in the blood, and so it did not result in toxicity.

The concern was that with such low, inadequate concentrations, early graft rejection could occur. Indeed, it has been shown that a TAC concentration of less than 8 ng/mL in the immediate post-KTx period in a treatment regimen with GCS and mycophenolic acid is an independent risk factor for acute rejection [27], and each decrease of 1 ng/mL during this time is associated with a 7.2% increase in the risk of acute rejection [28].

In the case described here, only the addition of fluconazole, a cytochrome P450 inhibitor that also participates in TAC metabolism, had the expected effect of achieving adequate drug blood levels. The effect of cytochrome P450 inhibitors and activators on the drug metabolism and many other substances is well known, which is why drug interactions, stimulants, herbs, spices, fruit, and even types of food (fat-rich foods delay the absorption of the drug) have such a strong influence on the CIN pharmacokinetics. Other cytochrome P450 inhibitors increasing TAC blood concentrations are calcium channel blockers (verapamil, diltiazem), commonly used as antiarrhythmic and antihypertensive medications [29]. They were not considered in the described case due to patient's tendency to bradycardia. It should also be remembered that the metabolism of GCSs occurs with the involvement of cytochrome P450, hence with a gradual reduction in their doses, a decrease in the clearance of TAC is observed, thus increasing its blood concentration. Large and frequently modified doses of GCSs used in the early post-transplant period have an additional effect on the variability of TAC concentrations [29]. In our case, in the later post-transplant period, when the minimum recommended doses of prednisone had been reached, the patient required lower doses of TAC.

Impaired drug disintegration and dissolution are also observed in patients undergoing bariatric surgery; liquid drug formulations are preferred over solid forms when available. In addition, film-coated tablets, including enteral tablets, delayed-release tablets, or extended-release tablets are not recommended, while immediate-release, crushable, or chewable tablets may show less difference in absorption in patients after bariatric surgery compared to the general population. The route of drug administration other than oral (intravenous, intramuscular, subcutaneous, vaginal, rectal, or intranasal) is also more favorable in these patients [16].

It is worth noting that if there are gastrointestinal disorders, rapid-release TAC capsules (after the drug has been spilled out of the capsule) can be administered sublingually. By this route, the drug is absorbed very well and requires a significant dose reduction (concentration monitoring required) due to the elimination of the first-pass effect. Similarly, with intravenous administration (continuous infusion required), a dose reduction of up to 1/5 of the due dose is necessary [14].

Interestingly, in the case described here, the use of the extended-release form of the drug administered against the recommendations of the SmPC, twice daily, led to an increase in TAC blood concentrations.

In the case of TAC treatment, the determination of drug concentrations is routine, so it is possible to adjust the dose individually; however, it should be borne in mind that the

concentrations of other drugs, including, for example, GCS, antibiotics, but also hypotensive drugs, are not determined and monitored, and the absorption and bioavailability of many of them may be significantly impaired.

SUMMARY

There are no dosage guidelines for drugs (including immunosuppressants) in patients after bariatric surgery. For KTx recipients after bariatric surgery, individualization and personalization of treatment is necessary: selection of the appropriate drug formulation, route of administration, and drug dosage preferably based on monitored therapy.

Also, due to the high instability of immunosuppressive drug concentrations in transplant recipients, after bariatric surgery, induction therapy is indicated.

CONFLICT OF INTEREST:

The authors declare that they have no competing interests in this case report. The authors have no financial or non-financial relationships that may have influenced the design, conduct, or reporting of this case report. The authors have no affiliations or involvement with any organization or entity that has a direct or indirect interest in the subject matter or materials discussed in this case report.

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