Glycemic Control After Kidney Transplantation Using Sensor-augmented Insulin Pump Therapy in a Patient with Slowly Progressive Type 1 Diabetes Mellitus

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Objective: Patients with advanced diabetic nephropathy benefit from kidney transplantation. We report a patient who showed improved glycemic control after kidney transplantation followed by sensor-augmented pump (SAP) therapy.
Methods: The patient was a 67-year-old man on hemodialysis for diabetic nephropathy associated with slowly-progressive type 1 diabetes mellitus. He underwent living-donor kidney transplantation, followed by introduction of SAP therapy for strict glycemic control.
Results: SAP therapy improved glycated hemoglobin and glycated albumin levels from 7.8% and 24.2% to 7.0% and 19.2%, respectively, and reduced the frequency of hypoglycemic episodes.
Conclusion: The case illustrates the usefulness of SAP therapy for post-kidney transplantation glycemic control.

Key words: sensor-augmented pump, transplantation, glycemic control

INTRODUCTION

The curative treatment for end-stage renal disease associated with diabetic nephropathy is simultaneous pancreas-kidney transplantation [1]. While revision of the Organ Transplant Law in Japan led to an increase in brain-dead donors, the number of donors remains insufficient. Because donors in most living-donor kidney transplants in Japan are close relatives, kidney transplants vastly outnumber pancreas transplants [2]. Therefore, Japanese patients with type 1 diabetes mellitus and kidney failure usually undergo only kidney transplant, followed by strict glycemic control with insulin therapy, and are placed on a waiting list for pancreas transplant. While poor post-transplant glycemic control can potentially result in damage of the transplanted kidney, evidence for post-transplant glycated hemoglobin (HbA1c) target level of 7.0–7.5% has not reached the recommendation grade and requires further discussion [3]. To achieve strict glycemic control in Japanese patients, who are less fortunate to receive simultaneous pancreas-kidney transplantation, diabetologists often use multiple daily injections (MDI) of insulin. Sensor-augmented pump (SAP) therapy, which was recently introduced in Japan, allows for continuous glucose monitoring, as well as the administration of predetermined amounts of basal insulin and additional adjustment doses of insulin as needed. The principle of this treatment is to mimic physiological insulin secretion [4, 5]. In the present case, SAP therapy was introduced after living-donor kidney transplantation, which improved both glycemic management and quality of life (QOL). This case could be a model for other diabetic kidney transplant patients in Japan. We report our experience with the hope it will encourage better collaboration between transplant surgeons and diabetologists.

CASE PRESENTATION

At about 27 years of age, the patient experienced profound weight loss over a short period of time. Around that time, he was found to have glucosuria on routine health check, but this was not followed up at a medical institution. At around 30 years of age, he visited a local physician for generalized fatigue and was diagnosed with diabetes mellitus, and was placed on an oral hypoglycemic agent. The glycemic control worsened with time and at age 40, he was treated with insulin. After vitreous hemorrhage at age 52 years, he was referred to our department and the Department of Ophthalmology for management of glycemic control. During hospitalization, he was found positive for glutamic acid decarboxylase (GAD) antibodies (4.3 U/mL [RIA]), and diagnosed with slowly progressive type 1 diabetes mellitus. Kidney function gradually deteriorated and reached end-stage renal disease at age 60, when hemodialysis was introduced and glycemic control was managed by the renal unit. At the age of

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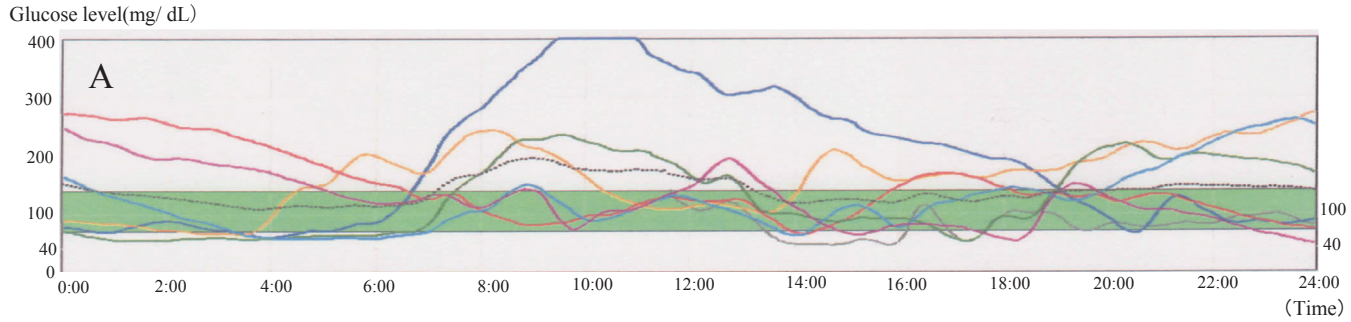
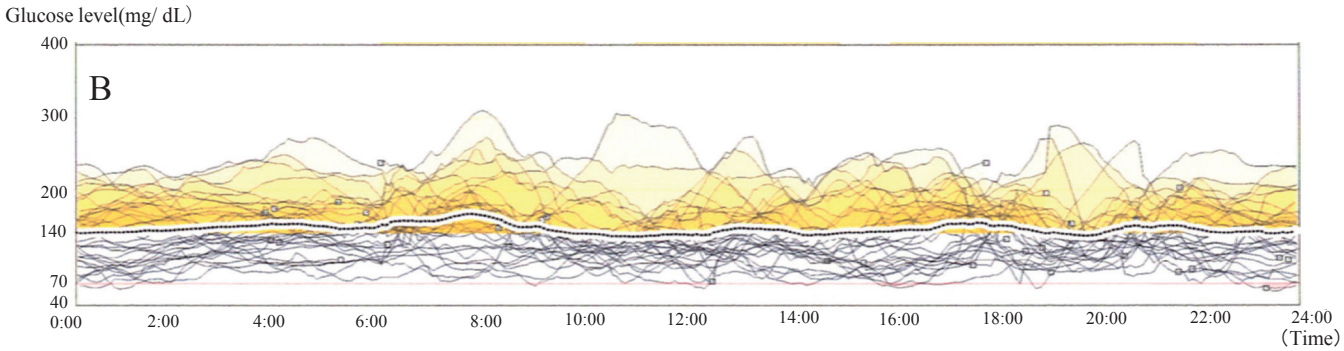


Mean glucose level: 139mg/ dL 、SD of glucose level: 72mg/dL
Hypoglycemic episode: 1 to 3times/day
Green-colored area: 70 to140mg/dL (target range)



Mean glucose level: 162mg/ dL l、SD of glucose level: 56mg/ dL
Hypoglycemic episode: 5 times/month
Dotted line: median sensor glucose level
Yellow-colored area: above 140mg/dL (above target range)

Fig. 1 Glucose profile before and after intervention.
A: Before kidney transplantation on MDI: CGMiPro®2.
B: After kidney transplantation on SAP.

66, the patient proposed living-donor kidney transplant with his wife as the donor and was referred to the Department of Transplant Surgery at our hospital. However, at that time, the glycemic control was poor with HbA1c and glycated albumin (GA) levels of 8.1% and 23.5%, respectively. Accordingly, he was transferred to our department for glycemic control. During hospitalization, the patient received details on dietary therapy, carbohydrate counting, and diabetes self-control using ultra-fast acting insulin before living-donor kidney transplantation. During hospitalization, the anti-diabetic treatment was adjusted to include 10 units of insulin degludec in the morning and before bed and 14 units of insulin aspart before each meal (self-regulated depending on sugar content).

In early October 20XX, the patient underwent ABO incompatible transplantation with his wife as the donor. Immunosuppressant therapy with mycophenolate mofetil (MMF), tacrolimus (FK), and methylprednisolone was initiated. Passage of urine was confirmed in the operating room and urinary volume was average thereafter. On postoperative day 2, serum creatinine (SCr) concentration fell to 4.96 mg/dL. Postoperative glycemic control was achieved with intravenous ultra-fast acting insulin in the intensive care unit, though it was gradually replaced with hypodermic injections.

At hospital discharge, the immunosuppressant therapy was prednisolone (5 mg), MMF (1,500 mg), and FK (3 mg); serum SCr level was around 1.25 mg/dL; treatment consisted of 10 units of insulin degludec in the morning and before bed, and 14 units of insulin aspart before each meal (self-regulated depending on sugar content); and postprandial blood glucose level was 70–280 mg/dL.

Frequent visits to the outpatient department after discharge showed stable renal function with SCr concentration around 1.5 mg/dL. Diabetes continued to be controlled using MDI, with HbA1c and GA around 6.8% and 20%, respectively. Despite this treatment, hyperglycemic and hypoglycemic episodes were frequently experienced, requiring frequent self-monitoring of blood glucose, supplementary insulin, or snacks. At that stage, SAP therapy was introduced to further stabilize glycemic control.

At the time of introduction of SAP, the settings for continuous subcutaneous insulin infusion (CSII) for basal insulin were 00:00–03:00: 0.2 units/h, 03:00–10:00: 0.5 units/h, 10:00–14:00: 0.4 units/h, 14:00–18:00: 0.65 units/h, and 18:00–24:00: 0.2 units/h, with a total daily dose (TDD) of 29.5 ± 10.8 units/day, total basal dose (TBD) of 9.5 units/day, and bolus insulin of 10–14 units, depending on the carbohydrate count. After discharge, the basal insulin was administered using the following protocol: 00:00–3:00: 0.9 units/h, 03:00–5:30: 0.8 units/h, 5:30–10:00: 1.0 units/h, 10:00–12:00: 0.5 units/h, 12:00–14:00: 0.75 units/

h, 14:00–18:00: 1.0 units/h, 18:00–22:00: 0.2 units/h, and 22:00–24:00: 0.9 units/h. Under this regiment, the TDD was 53.7 ± 9.9 units/day, and TBD was 11.35 units/day. Continuous glucose monitoring (CGM) confirmed blood glucose fluctuations before (Fig. 1A) and after introduction of SAP (Fig. 1B).

The HbA1c and GA improved to 6.5–7.0% and 18–20%, respectively, after introduction of SAP, relative to before SAP. Furthermore, the number of hypoglycemic episodes decreased from about five per week to 0–1 per week. These and other findings, as well as the reduced burden of glucose self-monitoring, were satisfactory to the patient and improved QOL.

DISCUSSION

The patient in the present case was found positive for GAD antibodies 25 years after the onset of diabetes mellitus and hemodialysis was applied 33 years after the onset. Unfortunately, blood insulin levels were not adjusted carefully in the dialysis unit and self-adjustment led to poor glycemic control. The patient was hospitalized for education on insulin adjustment and other matters before kidney transplantation and was treated by a diabetologist after the transplant. During the preoperative hospitalization, the patient underwent a full check of the insulin secretory capacity. Serum C-peptide level was below the sensitivity limit of the measurement procedure, which confirmed the poor insulin secretory capacity. Following kidney transplantation, kidney function was satisfactory, but the patient had difficulty in managing blood glucose levels with MDI, which included episodes of asymptomatic hypoglycemia and erratic glucose levels due to sudden changes in plans. SAP therapy was introduced to address this issue. The following individuals are covered by CSII in Japan: (1) adult patients with type 1 diabetes mellitus and unstable blood glucose levels under conventional MDI who present with hyperglycemia, hypoglycemia, asymptomatic hypoglycemia, or other issues; (2) patients with type 2 diabetes mellitus and markedly low insulin secretion capacity; (3) patients with type 1 or type 2 diabetes mellitus who require strict glycemic control and are pregnant or planning to become pregnant; and (4) pediatric patients with type 1 diabetes mellitus [6]. The present case was not in conflict with the above list, but dialysis patients have particular glycemic profiles that are different from regular diabetes patients, such as intraday fluctuations and day-to-day variations related to the use of dialysate as well as other factors [7]. Therefore, there is a need for active debate to determine the criteria for eligibility of dialysis patient as well as post-kidney transplant patients for CSII.

Compared with MDI, CSII can result in a better reproduction of physiological insulin secretion and, thus, leads to better glycemic control [8]. In addition, the introduction of CSII in type 1 diabetes mellitus has been reported to lower HbA1c levels compared to MDI without increasing hypoglycemic episodes [9, 10]. Moreover, the recent development of personal CGM has enabled self-management using sensor glucose (SG) levels, which reference real-time glucose measurements. This has tremendously improved glycemic control in patients with type 1 diabetes mellitus [11, 12]. In the present case, while post-kidney transplant glycemic control was satisfactory (HbA1c 6.1%, GA 18.4%), both HbA1c and GA may have been underestimated due to the administration of erythropoietin for postoperative anemia and the presence of mild hypoalbuminemia. In fact, 24-hour glucose fluctuations evaluated with the iPro2® (Fig. 1A) and self-monitoring of blood glucose (SMBG) levels during MDI therapy before the introduction of SAP therapy showed serious blood glucose spikes, ranging from 49 to 291 mg/dL. Three months after the introduction of SAP therapy, blood glucose level was 162 mg/dL with a standard deviation of 56 mg/dL, while HbA1c and GA levels were 7.0% and 19.7%, respectively, with improved anemia and hypoalbuminemia (Fig. 1B).

There is no clear HbA1c target for kidney transplant patients, although patients with frequent hypoglycemic episodes are advised to avoid targeting an HbA1c of 6% [3]. In our patient, asymptomatic hypoglycemia advanced to frequent hypoglycemic episodes, including nocturnal hypoglycemia. In type 1 diabetes mellitus, severe hypoglycemia is associated with increased risk of cardiovascular disease and overall mortality rate [13]. Certain Japanese institutions target HbA1c level of 7% to avoid hypoglycemia several months after kidney transplantation (personal communication). Currently, the SAP used in Japan is the Medtronic MiniMed® 620G System. This device displays SG values and insulin is automatically-injected when blood glucose levels from SMBG are entered. The MiniMed® 620G System can predict certain glucose level or be set to sound an alarm when that level is reached, but it does not stop insulin administration. Compared to MDI therapy without CGM, the frequency of hypoglycemic episodes decreased with SAP therapy, but severe hypoglycemia did not decrease significantly [14]. One possible reason for the latter observation could be that the alarm that sounded for nighttime asymptomatic hypoglycemia failed to wake up the patient, which meant that insulin continued to be injected, leading to severe hypoglycemia. The development of Medtronic MiniMed® 640G System, which is designed to stop insulin injection upon the detection of hypoglycemia, and the MiniMed® 670G System, which has an automatic injection function for hyperglycemia, is expected to reduce both extreme and severe hypoglycemia [15, 16]. The present case never required emergency management for severe hypoglycemia and the alarm function of the MiniMed® 620G System reduced the frequency of asymptomatic hypoglycemia from almost daily to about five episodes per month.

Patients with type 1 diabetes mellitus and low insulin secretory capacity require insulin therapy to maintain life. Nevertheless, insulin therapy has a major impact on the daily lives and social activities of patients. In particular, patients with end-stage renal disease who require dialysis face a variety of time and space restrictions that reduce their QOL [17, 18]. When treating patients with end-stage renal disease who require insulin therapy, physicians must be aware of the need to improve QOL when providing medical care. The UKPDS 37 study found a lower QOL among patients who experienced hypoglycemia [19]. In Japan, Ishii *et al.* [20] reported that discovering hypoglycemic episodes was key to achieving higher QOL levels during insulin therapy. Both studies found that the

difficulty of addressing nocturnal hypoglycemia had a particularly large psychological burden on patients. This suggests that SAP therapy, with a nighttime alarm so patients can deal themselves with hypoglycemia, can reduce this burden. In the present case, the patient stated that the reduced number of hypoglycemic episodes improved QOL.

One major factor that can hinder the introduction of SAP or CSII therapy is cost [21]. As described above, SAP or CSII therapy can improve glycemic management, but the penetration rates of these therapies in Japan are low overall not only among kidney transplant patients, with cost thought to be a major reason. In Japan, patients who need dialysis are designated as having severe physical disability, and the medical expenses subsidy program for severely disabled people in many local governments of this country covers the medical costs. In the present case, because living-donor kidney transplantation was performed after the introduction of hemodialysis, this designation continued even after the transplant. Thus, a smaller financial burden was one reason why SAP therapy could be selected. Going forward, diabetologists, who can share information with both patients and general practitioners, will likely become even more significant source of information on improvement of QOL and reducing financial burdens on the patients.

In summary, while the curative treatment for type 1 diabetes mellitus is simultaneous pancreas-kidney transplantation, there are long-term problems with such treatment, such as the lack of donors. SAP therapy may be useful for glycemic control and improvement of QOL not only after kidney transplantation but also in patients with type 1 diabetes who require dialysis or kidney transplant; thus, SAP should be considered as a treatment option. Going forward, nephrologists, transplant surgeons, and diabetologists should work together with respect to this matter.

CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this article.

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