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CASE REPORT

Continuous subcutaneous insulin pump treatment associated with absence of recurrent kidney allograft diabetic nephropathy

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Introduction

Improved glycemic control with a bionic pancreas and recent safety data of a wearable artificial pancreas may be relevant for kidney transplant recipients with type 1 diabetes [1, 2]. Diabetes is a major risk factor for end-stage renal disease, and the DCCT trial showed that tight glycemic control is superior to conventional insulin therapy to prevent complications of type 1 diabetes, including diabetic nephropathy [3]. Moreover, continuous subcutaneous insulin pump infusion partially prevented early diabetic nephropathy in native kidneys in another 3-year follow-up study which included kidney biopsies [4].

In kidney allografts, the risk of recurrent biopsy-proven diabetic nephropathy is almost 100 % after 10 years of follow-up, and histological diabetic lesions can be observed as soon as 2 years after transplant [5]. Kidney–pancreas transplantation with its associated euglycemia can prevent recurrent diabetic nephropathy in the allograft [6, 7]. However, kidney–pancreas transplantation is associated with significant morbidity, and donor organ shortage limits its widespread application [8]. Islet after kidney transplantation can also potentially reduce long-term diabetic complications; however, the rate of insulin independence after islet transplantation remains significantly lower as compared to full pancreas transplantation [9].

Case report

A male patient underwent deceased donor kidney transplantation (without pancreas transplantation) at our institution for type 1 diabetic nephropathy in 1999, at the age of 41. Before transplantation, he suffered from a diabetic proliferative retinopathy and polyneuropathy of lower extremities, but without evidence of cardiac involvement. After discussion with the patient and his primary care physician, simultaneous kidney–pancreas transplantation was not contemplated because of its potential morbidity. His immunosuppressive regimen consisted of induction with basiliximab 20 mg at day 0 and day 4. His maintenance therapy was cyclosporine and prednisone, and mycophenolate mofetil was added in 2012.

Since his kidney transplant, he was on continuous subcutaneous insulin pump therapy and he was able to achieve near-euglycemia over the years by doing 6–8 glycemic controls per day (Figs. 1 and 2). His median glycated hemoglobin level was 6.7 % (±0.5 %) over a 10-year period ($n = 22$ measurements), i.e., below the recommended target for adults from the American Diabetes Association.

In late 2010, he developed anti-HLA class II donor-specific alloantibodies against the antigen DQ7.

In September 2012, because of a progressive rise in serum creatinine from 115 to 155 µmol/l with new-onset hypertension, he underwent a kidney allograft biopsy. Histology demonstrated chronic active antibody-mediated (humoral) rejection of the kidney allograft, associated with tubulitis (with CD3 T cells) and few interstitial CD20 B cells. Interestingly, there were no recurrent diabetic

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nephropathy lesions and, in particular, no Kimmelstiel–Wilson pattern in the glomeruli.

In addition to the lack of diabetic lesions in the kidney allograft, there were no cardiovascular events since his kidney transplant. Moreover, his retinopathy and his polyneuropathy had remained clinically stable, with no documented foot infections or ophthalmologic complications over the years.

This unique observation indicates that maintaining long-term glycemic values within the normal range with the use of a continuous subcutaneous insulin pump can be associated with absence of recurrent diabetic nephropathy after kidney transplantation. To our knowledge, this is the first report that demonstrates the long-term efficacy of using such a strategy in a type 1 diabetic kidney recipient. Since tight glycemic control requires considerable self-management efforts by the patients in their daily life, this observation may serve also as a motivational support for such a strategy. Hence, the currently observed improvements in "artificial pancreas" technology may become extremely important for kidney transplant recipients with insulin-dependent diabetes mellitus, possibly obviating the need for pancreas transplantation in the near future.

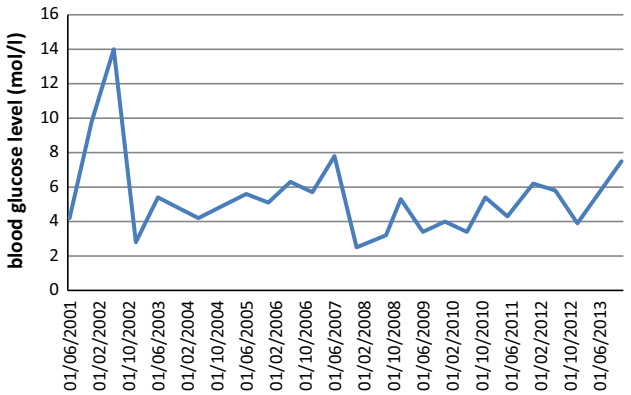

Fig. 1 Outpatient clinical morning glycemia over the years. Graphic showing that since his transplantation, the morning glycemia of the patient was in the range of euglycemia

It should be noted that other new therapeutic strategies are also being investigated to prevent diabetic nephropathy for patients with new-onset type 1 diabetes. For example, a novel therapy is the use of autologous nonmyeloablative hematopoietic stem cell transplantation, with antithymocyte globulin and cyclophosphamide, which can result in insulin independence at 6 months [10]. However, such protocol has not been tested in the transplant setting.

Another potentially effective strategy in diabetic transplant recipients may be the use of inhibitors of the B7-1 receptor. B7-1 expression, a podocyte receptor, has been linked with the progression of kidney disease in a wide variety of glomerular diseases including diabetic nephropathy [11]. Inhibitors of the B7-1 receptor can decrease proteinuria in experimental models. Belatacept is already approved in renal transplantation to replace the use of calcineurin inhibitors. Thus, the use of belatacept together with a continuous subcutaneous insulin pump could possibly improve the life span of allografts in diabetic recipients. The possible benefits of this approach to reducing the recurrence of diabetic nephropathy need to be investigated prospectively. Finally, experimental stem cell

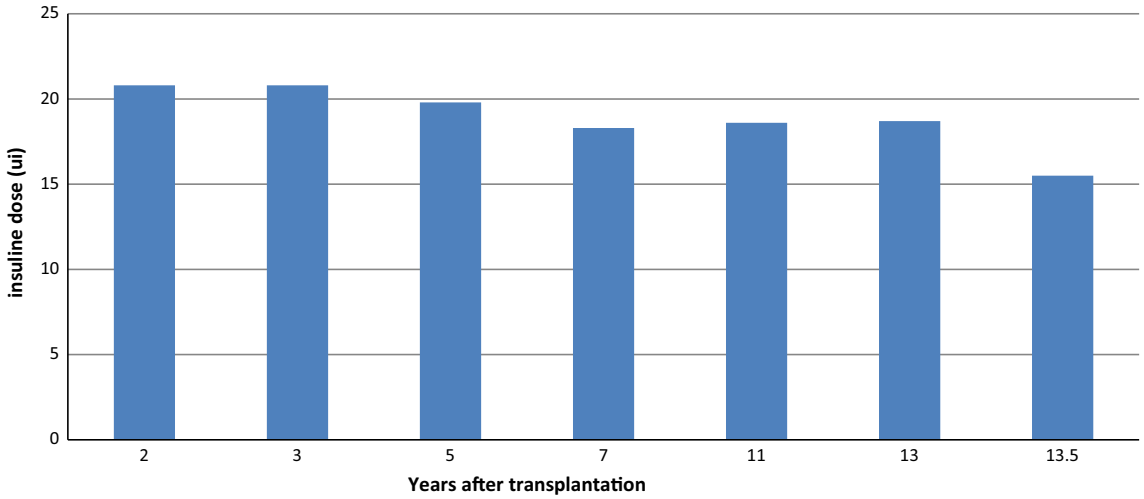

Fig. 2 Daily basal insulin pump debit over the years. Graphic showing the basal insulin pump debit since the patient transplantation, which was stable over the years

infusion (embryonic or cord blood cells) has showed preliminary promising results in murine models [12], However, it is too soon to consider such an approach as an alternative to conventional therapies.

Conflict of interest The authors report no conflict of interest.

Ethical standard All human studies have been reviewed by the appropriate ethics committee.

Human and animal rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent disclosure Informed consent was obtained from all patients for being included in the study.

References

1. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Damiano ER et al (2014) Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 371:313–325. doi:10.1056/NEJMoa1314474
2. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Doyle FJ 3rd et al (2014) Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 37:1789–1796. doi:10.2337/dc13-2076
3. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Eng J Med 329:977–986
4. Bangstad HJ, Osterby R (1994) Hanssen KF (1994) Improvement of blood glucose control in IDDM patients retards the progression of morphological changes in early diabetic nephropathy. Diabetologia 37:483–490
5. Mauer SM, Steffes MW, Connett J, Najarian JS, Sutherland DE, Barbosa J et al (1983) The development of lesions in the glomerular basement membrane and mesangium after transplantation of normal kidneys to diabetic patients. Diabetes 32:948–952
6. Wilczek HE, Jaremko G, Tydén G, Groth CG et al (1995) Evolution of diabetic nephropathy in kidney grafts. Evidence that a simultaneously transplanted pancreas exerts a protective effect. Transplantation 59:51–57
7. Bohman SO, Tydén G, Wilczek H et al (1985) Prevention of kidney graft diabetic nephropathy by pancreas transplantation in man. Diabetes 34:306–308
8. Gremizzi C, Vergani A, Secchi A et al (2010) Impact of pancreas transplantation on type 1 diabetes-related complications. Curr Opin Organ Transplant 15:119–123. doi:10.1097/MOT.0b013e32833552bc
9. Lehmann R, Graziano J, Gerber PA et al (2015) Glycemic control in simultaneous islet-kidney versus pancreas-kidney transplantation in type 1 diabetes: a prospective 13-year follow-up. Diabetes Care. doi:10.2337/dc14-1686
10. D'Addio F, Vasquez A, Fiorina P et al (2014) Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis. Diabetes 63:3041–3046. doi:10.2337/db14-0295
11. Fiorina P, Vergani A, Sayegh MH et al (2014) Role of podocyte B7-1 in diabetic nephropathy. J Am Soc Nephrol 25:1415–1429. doi:10.1681/ASN.2013050518
12. D'Addio F, Trevisani A, Fiorina P et al (2014) Harnessing the immunological properties of stem cells as a therapeutic option for diabetic nephropathy. Acta Diabetol 51:897–904. doi:10.1007/s00592-014-0603-1