

Teaching Point
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C-peptide and combined kidney pancreas transplantation

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Introduction

Simultaneous transplantation of kidney and pancreas (SKP) is an excellent treatment option for patients with type I diabetes mellitus with end-stage renal failure. The risk associated with the procedure is somewhat higher than that with transplantation of a kidney alone. This excess risk relates to a higher likelihood of rejection, necessitating on average higher levels of immunosuppression, as well as an increased surgical risk regarding thrombosis of the pancreatic graft and infection. In suitable patients, however, this excess risk is offset by the fact that successful SKP ensures a life free of dialysis and insulin. Traditionally, SKP has been reserved for patients with type I diabetes mellitus while type II diabetes has been regarded as a contraindication. Most transplant centres also believe that C-peptide levels are helpful to distinguish between the two and require a C-peptide assay as part of the workup for SKP. In this regard, we present a case that provided a surprise during workup for SKP. We briefly discuss the relevant literature and highlight current controversies regarding C-peptide levels and workup for SKP. The case presented here initially deceived us after numerous seasoned clinicians all claimed that he had type I diabetes. It was only after his markedly elevated C-peptide levels came back that we refuted a diagnosis of type I diabetes and abandoned the plan of SKP.

Case

A 27-year-old man with a 15 year-history of diabetes was referred to us for SKP workup. He had congenital hypoplasia of the right kidney with a normal-sized left kidney. Gradual deterioration of his renal functions was assumed to be secondary to diabetic nephropathy. He also had diabetic retinopathy but no overt vascular complications. Hence, a renal biopsy had never been performed and

also because he had a *de facto* solitary kidney. The patient started haemodialysis in June 2007. Further history taking revealed that he has also had idiopathic necrosis of the femoral epiphysis. Finally, he had also been diagnosed with mild and stable olivo-ponto-cerebellar atrophy (OPCA). He was wheelchair dependent although he could mobilize to a limited extent at home. He had no family history of note. He lived with his girlfriend who was also his carer. His medication included insulin, aspirin, one alpha calcidol and calcium acetate. Examination showed a cheerful young man in a wheelchair without signs of cardiac or peripheral vascular disease. He was 150 cm in height and weighed 63.3 kg, giving him a body mass index (BMI) of 28.1. Echocardiogram and thallium scan were normal and a further set of investigations did not reveal any contraindications for SKP. An opinion from his neurologist was also sought, who reassured us that the patient's OPCA was stable and, in the worst case, only slowly progressive. Finally, his fasting C-peptide level was checked. The first test came back markedly elevated at 3252 (normal 190–990 pmol/l). A repeat level done after 3 months came back at 1725 pmol/l. The diagnosis of type I diabetes was questioned, workup for SKP was abandoned and evaluation for kidney alone transplantation was commenced. Live donor workup of the family was also started.

Discussion

The benefit of simultaneous kidney–pancreas transplantation (SKP) is freedom from both insulin therapy and dialysis and thus an improved quality of life. Long-term survival in contemporary series is excellent [2]. Normalization of fasting glucose and glycosylated haemoglobin levels is associated with prevention of progression and partial reversal of the complications of diabetes [3]. However, SPK is associated with a higher risk of complications and rejection when compared to kidney transplantation alone (KTA) [4]. On average, SKP patients therefore require more intense immunosuppression than KTA patients. The excess risk also relates to the more challenging nature of the surgery itself with the potential for vascular thrombosis of the

pancreas graft, infection, bleeding and the need for surgical intervention or even removal of the transplanted pancreas. Contemporary 1-year graft survival rates for SKP are in excess of 80% for pancreas survival and 90% for kidney survival. Finally, owing to the underlying disorder and its severity, average SKP recipients have a substantial vascular risk profile anyway. Therefore, patient selection is crucial to successful SKP. In this case workup for SPP was abandoned on the basis of considerably elevated C-peptide levels. Was that justified? The case discussed here boils down to two issues: firstly, should SKP be limited to patients with type I diabetes, and secondly, does C-peptide discriminate between the two in patients with renal failure?

Traditionally, patients with type I diabetes, which are younger than 50 years and who are approaching ESRD or already on dialysis, are regarded as suitable for SKP. The current UK guidelines require candidates to be insulin-dependent type I diabetics and be either on dialysis, or have chronic kidney disease and anticipated to require dialysis within 6 months [5]. It is worthwhile to remember that there are various options for such patients. It was previously thought that only a HLA identical live-donor kidney transplant with subsequent isolated pancreas transplantation was equivalent to SKP [4]. Recent US data, however, suggest that live-donor KTA may be equally effective if not superior to SKP even if not HLA identical [6]. The role of islet cell transplantation remains yet to be established. At present, this procedure is usually performed in patients with brittle type I diabetes but without renal failure.

It seems straightforward from a pathogenetic point of view to limit SKP to patients with type I diabetes: transplantation of insulin-producing islet cells should work best if the absence of insulin is the underlying problem. Accordingly, current guidelines in the UK [5] limit SKP to patients with type I diabetes. A seminal but earlier review article from the United States concurs on this issue [4]. However, this view has been challenged. The Minneapolis group reported on a cohort of 17 patients with type II diabetes who underwent SKP, pancreas alone or pancreas after kidney transplantation [7] although the authors admit that they did not necessarily identify the patients having type II diabetes prior to surgery [7]. In summary, it is probably fair to conclude that most institutions perform SKP only in type I diabetes patients. This is corroborated by reports on current practice. Friedman and Friedman sought for patients with type II diabetes who underwent SKP and reported that these account for only 1.8% of SKP procedures performed in the USA [8]. But how to distinguish between the two types of diabetes in renal failure? The history may be incomplete, particularly when it comes to the interesting features, such as BMI at time of presentation with diabetes, or insulin requirements early on. Conversely, BMI at the time of transplant assessment would not be very helpful, as co-morbidity and the effects of renal failure itself will obviously confound it.

C-peptide is a 31 amino-acid polypeptide that is generated during the process of insulin biosynthesis within the pancreatic beta-cell [9] (Figure 1). Hence, insulin and C-peptide are released into the portal circulation in an equimolar ratio. C-peptide levels may be measured in blood or urine by a radio-immunoassay. Of note, insulin is rapidly re-

moved from plasma by liver and kidney. The latter clears insulin via two mechanisms: the first mechanism is glomerular filtration and subsequent luminal reabsorption of insulin by proximal tubular cells by means of endocytosis. The second involves diffusion of insulin from peritubular capillaries and subsequent binding of insulin to the membranes of tubular cells. Both liver and kidney are very effective in clearing insulin from plasma; hence insulin plasma levels fluctuate substantially with a half-life of 6 min. In contrast, C-peptide has a half-life of 30 min, which is why C-peptide is usually measured to evaluate endogenous insulin secretion. In this regard, C-peptide is particularly useful in the evaluation of fasting hypoglycaemia: it helps to distinguish between insulinomas (where insulin and C-peptide are released concurrently) and factitious hypoglycaemia (where C-peptide is absent). Of note, C-peptide is not present in pharmaceutical preparations of insulin. C-peptide levels are also used to monitor graft function in islet cell transplantation.

First, we need to appreciate that C-peptide levels are influenced by renal function. Indeed, C-peptide is eliminated by glomerular filtration. Hence, the usual close relationship between endogenous insulin production and C-peptide levels is somewhat disturbed in renal failure [10]. However, we also know from large trials that 15 years after the diagnosis of type I diabetes very few patients exceed C-peptide levels of 200 pmol/l, even after stimulation with a mixed carbohydrate meal [11] and probably even in renal failure. These data are very much in keeping with our own experience in SKP candidates: the overwhelming majority of such patients indeed have undetectable C-peptide levels, in keeping with longstanding type I diabetes. Covic and co-workers have suggested an algorithm for phenotyping diabetic patients with renal failure. According to their scheme, our patient would clearly have type II diabetes [12]. Becker and co-workers, reviewing the largest body of single-centre experience with SKP at the University of Wisconsin in the United States, also list low C-peptide levels as a criterion for eligibility to SKP [4]. The UK guidelines state that C-peptide levels should be done if needed although it is not clarified further [5]. Guidelines in the United States, on the other hand, are very strict. Medicare will only cover SKP or pancreas alone transplantation if the C-peptide levels are less or equal to 110% of the laboratory's lower limit of normal [13]. However, it must be borne in mind that these guidelines may be influenced by an economical assessment as well.

More recently, this view has been challenged. Light and co-workers studied data from 136 SKP recipients and found no influence of pre-transplant C-peptide levels on the outcome of SKP [14]. The authors conclude that SKP should be offered to patients regardless of pre-transplant C-peptide levels. These data are interesting but not yet conclusive and need to be reproduced by other centres. Furthermore, the patients with higher C-peptide levels in that study may be highly selected and their findings may be difficult to extrapolate to the population of diabetics with renal failure at large.

For now, we therefore tend to adhere to the more conservative view that SKP should be more or less limited to patients with type I diabetes and those with low C-peptide.

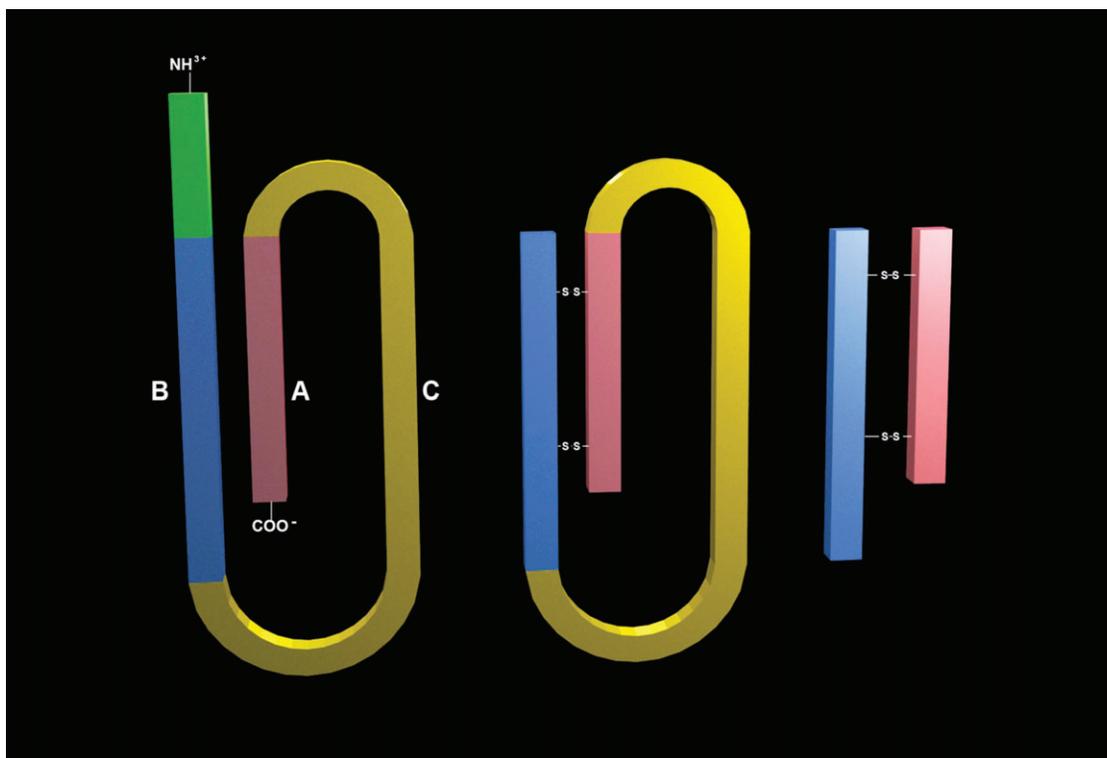


Fig. 1. Structure of preproinsulin, proinsulin and insulin. A denotes the A chain (red). B denotes the B chain (blue). C denotes C-peptide. Redrawn after [9]. C-peptide is a 31 amino-acid polypeptide that is generated during the process of insulin biosynthesis within the pancreatic beta-cell [9]. Insulin consists of two chains that are linked by disulfide bonds. Preproinsulin is transcribed as a 110 amino acid chain and contains a terminal signal sequence (green). On entry into the endoplasmic reticulum, cleavage of the signal sequence (green) turns preproinsulin into proinsulin. Disulfide bonds between the alpha and beta chain are now formed while a connecting peptide chain (C-peptide) connects the two. Shedding of the C-peptide finally results in insulin.

We would also argue that SKP should be offered to those who are most likely to benefit. From a pathogenetic point of view, C-peptide-deficient individuals should benefit the most. We do not think that the extra risk of SKP (compared to KTA) should be borne by patients in whom peripheral insulin resistance casts doubt on the success of the procedure. Esmatjes and co-workers seem to concur and emphasize the utility of C-peptide levels to phenotype SKP candidates [1]. Undoubtedly, more precise means of phenotyping would be very desirable. It is tempting to think of an underlying syndrome in our patient with diabetes, short stature and OPCA, but we could not identify any. Maturity onset diabetes of the young (MODY) comes to mind as a disease where a young patient presents with a syndrome that resembles type II diabetes. However, MODY is genetically heterogeneous and we did not suggest genetic testing because it would not have changed our management of this patient. It is worthwhile to know that the American Diabetes Association (ADA) has recently proposed a new classification for diabetes [15].

Teaching points

- (i) Simultaneous kidney pancreas transplantation is an excellent treatment option for younger renal failure patients with type I diabetes.

- (ii) The role of pancreas transplantation in selected patients with other forms of diabetes remains yet to be established.
- (iii) C-peptide is a by-product of insulin synthesis and released in equi-molar amounts; it can be used to monitor endogenous insulin secretion, since insulin itself is difficult to measure.
- (iv) C-peptide undergoes glomerular filtration; hence C-peptide levels depend on renal function.
- (v) C-peptide levels are a suboptimal test to phenotype diabetic patients with renal failure although type I diabetes seems unlikely if a SKP candidate presents with markedly elevated C-peptide levels.

Conflict of interest statement. None declared.

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