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Glycaemic control and graft loss following renal transplantation

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Introduction

Diabetes is the single most common reason for end-stage renal disease (ESRD) in the Western world. Currently, one-quarter of all renal transplant patients and almost half of all patients entering renal replacement programs have diabetes [1]. In addition, many patients without diabetic nephropathy show glucose intolerance and manifest hyperglycaemia following transplantation. We have recently reported the development of significant fasting hyperglycaemia (>8.0 mmol/l) immediately following transplant surgery in 73% of patients without diabetes [2]. Moreover, a majority of patients continue to be hyperglycaemic long after surgery. Careful attention to glycaemic control is therefore important for most patients undergoing renal transplantation because, in addition to reductions in post-operative infection [3] and prevention of the vascular complications of diabetes, there is evidence that glycaemic control also contributes to the main causes of allograft loss.

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Acute rejection

Patients with diabetes have an increased incidence of acute rejection following renal transplantation (Figure 1) [4]. We have shown in a multivariate analysis that peri-operative glycaemic control independently predicts acute rejection in recipients with diabetes [3]. Patients who subsequently developed allograft rejection had significantly worse glycaemic control in the hours following transplant surgery (Figure 2). Only 11% of diabetic patients with optimal control (mean glucose concentration <11.2 mmol/l over the first 100 h) had a rejection episode, compared to 58% with poor early control (mean glucose concentration >11.2 mmol/l over the first 100 h). Similar findings were present in a parallel non-diabetic cohort [2] (Figure 3).

We postulate that hyperglycaemia has important effects both on inflammation and on immunity in the early engraftment period. When tissue is

newly exposed to hyperglycaemia, it reacts with an exaggerated inflammatory response to ischaemia/reperfusion [5], enhanced expression of allo-antigens and co-stimulatory molecules [6], increased endothelial activation [7], and leukocyte adhesion and transmigration [8]. These are all known stimuli that may promote the rejection process.

Post-operative hyperglycaemia is also a marker for insulin resistance, characterized by hypertension, dyslipidaemia, hyperinsulinaemia, and increased circulating levels of leptin, TNF-α, IL-1, IL-6, and IL-12. These, by themselves or in combination with hyperglycaemia, may enhance allograft injury or rejection. Patients with insulin resistance may also possess abnormalities of the innate immune system, including an augmented cytokine responsiveness manifested by an increased CRP, which is also a risk factor for rejection [9]. Achieving and maintaining good glycaemic control both improves insulin resistance and reduces many of these pro-inflammatory mediators and markers, including CRP [10]. Although the restoration of a normal immunological milieu by aggressive glycaemic control prior to transplantation would seem prudent, there are currently no studies confirming the utility of this strategy. Intensive glycaemic control prior to conception reduces the risk of developmental abnormalities in patients with diabetes [11]. We believe that preparation for a transplant deserves to proceed in exactly the same way.

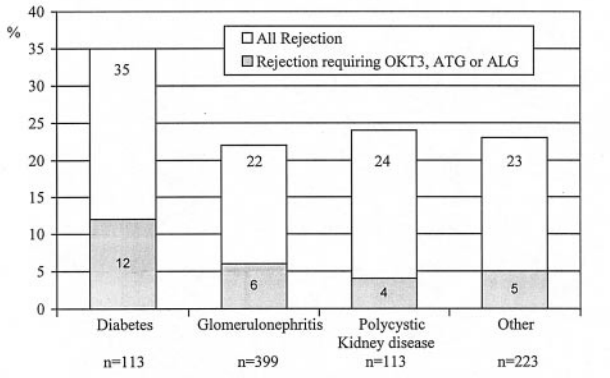

Fig. 1. Incidence of acute rejection during the first month in patients receiving their first cadaveric renal grafts (CD1) according to primary renal disease between 1997 and 2000 (ANZDATA) [4].

Delayed graft function

Early allograft injury, as manifested by a delay in function, has been linked both to acute rejection and to poor long-term graft survival. The incidence of delayed graft function is increased in patients with diabetes [12], although there are no studies examining its relationship to glycaemic control. Hyperglycaemia worsens renal ischaemic injury in experimental models [13]. The generation of lactate and reactive oxygen species is augmented in hyperglycaemia [14]. Re-perfusion injury may also be increased [15]. The occlusion-then-reperfusion that follows transplantation is functionally similar to ischaemic injury in other organ systems. Comparable studies in patients following myocardial infarction have shown a direct relationship between glycaemic control and the extent and outcome of ischaemic injury [16].

Chronic allograft dysfunction

Chronic rejection is the main cause of graft loss and more likely in patients with diabetes [17]. In

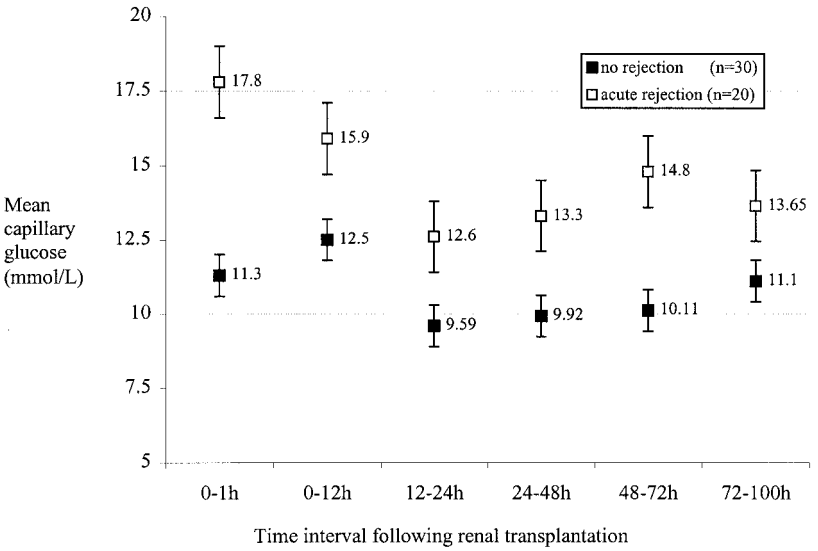

Fig. 2. Mean capillary glucose concentration during the first 100 h following surgery in diabetic patients with and without subsequent acute allograft rejection within 20 days of renal transplantation [3].

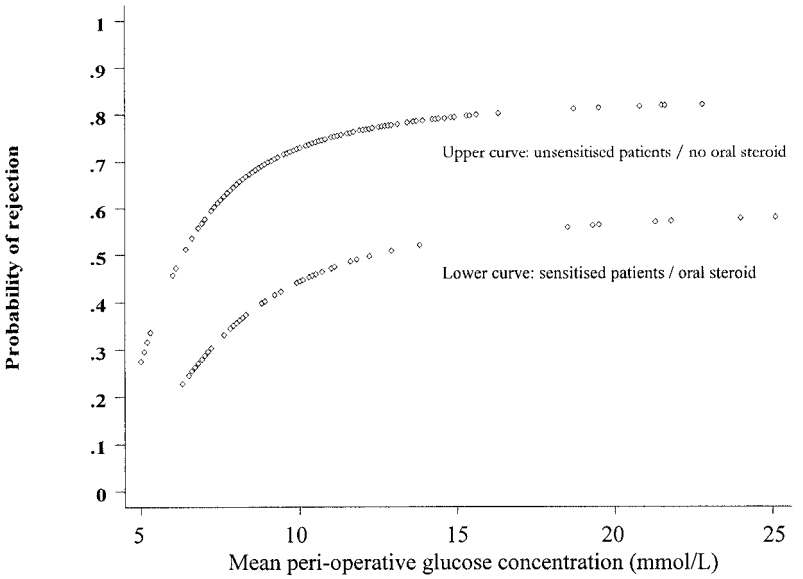

Fig. 3. Fractional polynomial showing the probability of rejection in sensitized (PRA >50, triple therapy) and unsensitized (PRA <50, double therapy) CD1 patients *vs* the mean capillary glucose concentration in the 100 h following transplant surgery ($n=230$) [2].

addition, patients who experience acute rejection, delayed graft function, hypertension, or dyslipidaemia, all of which may be influenced by hyperglycaemia, have an increased risk of chronic allograft dysfunction [18]. The pathogenesis of chronic allograft dysfunction is unclear. It is thought that both immunological and non-immunological mechanisms may contribute to progressive graft dysfunction. Histological features include fibrosis, intimal proliferation, and vascular occlusion. In experimental models, hyperglycaemia is able to potentiate each of these processes. In particular, glomerular hyperfiltration and renal synthesis of TGF-β are increased in chronic allograft dysfunction [17] and augmented by hyperglycaemia. Hyperglycaemia may also enhance drug toxicity from cyclosporin A [19], possibly via enhanced apoptosis, matrix formation and synthesis of TGF-β and PKC. Intensive glycaemic control in diabetic recipients, on the other hand, reduces arteriolar hyalinosis and glomerular and mesangial volumes compared to standard control [20]. Patients with prolonged graft survival have significantly lower serum lipid and fasting glucose levels both before and after transplantation [21]. The risk of late graft failure has been associated with the serum triglyceride concentration, which is also closely linked to glycaemic status.

Disease recurrence

Histological features of diabetic nephropathy recur in most if not all patients, following renal transplantation [22]. Renal function is said to decline at a slower rate from recurrent nephropathy than in the native diabetic kidney [23], although the impact of early management of hypertension, glucose and lipid levels in the transplant population makes this hard to confirm. Because clinically significant diabetic nephropathy recurs only slowly, and because until recently long-term survival of patients with diabetes was uncommon, the impact of recurrence on graft outcomes is also difficult to assess. As survival statistics improve, the potential impact of recurrent nephropathy may become increasingly important. It is thought that recurrent nephropathy may result in graft loss in less than 5%, although greater rates have been reported [22].

The presence of diabetic changes in allograft tissue has largely been attributed to glycaemic control, since patients with post-transplant diabetes may develop nephropathy, and diabetic lesions can be prevented by normoglycaemia with a concurrent pancreatic transplant or with intensive insulin therapy. Reversal of diabetic changes in native kidneys following pancreas transplantation has been described [24]. Kidneys with diabetic nephropathy when transplanted into non-diabetic recipients may also undergo histological reversal [25]. Both the degree of histological change and the rate of progression of recurrent disease may be proportional to glycaemic control.

Glycaemic control before and after transplantation

Because standard post-transplant management is directly diabetogenic, it is not easy to achieve glycaemic control following transplantation. Non-diabetic recipients who are treated with steroids show an insulin resistance comparable to diabetic patients [26]. In fact, a slow infusion of 5% dextrose may result in significant hyperglycaemia in a non-diabetic patient on steroids [27]. Regimens to reduce steroid use, or to

replace them with less-diabetogenic steroids such as deflazacort may reduce the incidence of dys-glycaemia without compromising immunosuppression [28]. A steroid avoidance programme (double therapy) at our centre has also been associated with good long-term outcomes [29].

Tacrolimus causes diabetes in up to 40% of patients, and significantly affects insulin requirements in patients with established diabetes [30]. Cyclosporin increases insulin resistance and may antagonize the effects of sulphonylurea hypoglycaemic agents [31]. A healthy allograft kidney clears insulin and hypoglycaemic drugs as well as synthesizing glucose. Improved appetite and weight-gain following renal transplantation may also contribute to hyperglycaemia.

Many dialysis patients with diabetes require little or no insulin to prevent hyperglycaemia. However, intensive control is nonetheless troublesome. Swings to hypoglycaemia may become an increasing problem as the half-life of glucose-lowering agents becomes prolonged and the gluco-synthetic properties of the kidneys decline. In addition, falsely elevated HbA_{1c} concentrations in ESRD may lead to overzealous attempts to reduce hyperglycaemia. It can also be mistakenly supposed that hyperglycaemia is no longer a problem in ESRD, because patients without renal function do not develop polyuria and dehydration, and advanced diabetic complications are often perceived as irreversible. Regrettably, the difficult balance of risk and benefit leads many physicians to settle for less than optimal glycaemic control.

Conclusions

Because the overall outcomes following combined simultaneous kidney–pancreas transplantation appear to be better than for kidney-alone transplantation, possibly as a result of better glycaemic control [32], it has been suggested it that should be regarded as the 'gold standard' treatment for patients with insulin-dependent diabetes and ESRD. However, the majority of diabetic patients requiring renal replacement have non-insulin-dependent diabetes [1] and the majority of insulin-dependent patients reaching ESRD are unsuitable for pancreas surgery. In consequence, efforts to reproduce outcomes similar to those following pancreas transplantation must still depend largely on conventional interventions aimed at achieving optimal glycaemic control. For the patient with diabetes, a new commitment to glycaemic control should accompany a new kidney as an important way to improve both patient and graft survival.

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