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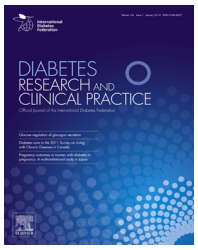

Invited Review

Is diabetic nephropathy reversible?

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ABSTRACT

The lesions of diabetic nephropathy have been considered to be irreversible. Pancreas transplantation is the only available treatment able to restore long-term normoglycemia without exposing the patients to the risks of severe hypoglycemia; thus allowing testing the effects of very long-term euglycemia in preventing, halting and reversing diabetic nephropathy. Pancreas transplantation, performed simultaneously or shortly after kidney transplantation in patients with type 1 diabetes prevents the recurrence of diabetic glomerulopathy lesions. To test whether diabetic nephropathy lesions are reversible in humans, we studied renal structure before and 5 and 10 years after pancreas transplantation alone in eight non-uremic patients with long-term type 1 diabetes, who had mild to advanced diabetic nephropathy lesions at the time of transplantation. We observed that, despite prolonged normoglycemia, diabetic glomerular lesions were not significantly changed at 5 years post pancreas transplantation. In contrast, glomerular lesions were markedly improved after 10 years; indeed in most patients glomerular structure was normal at 10-year follow-up. We reported similar findings also for tubular and interstitial lesions. Thus this study demonstrated, for the first time in humans, that the lesions of diabetic nephropathy are reversible and that the kidney can undergo substantial architectural remodeling upon long-term normalization of the diabetic milieu.

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1. Introduction

Diabetic nephropathy is a common microvascular complication of both type 1 and type 2 diabetes and is the single most common cause of end stage renal disease (ESRD) in adults in western countries [1,2]. In the last decades there has been a dramatic increase in the proportion of ESRD patients affected by diabetes, and this increase is largely due to type 2 diabetes. The clinical manifestations of diabetic nephropathy, proteinuria, increasing blood pressure and decreasing glomerular filtration rate (GFR) are the same in type 1 and type 2 diabetes [3], but the renal lesions underlying renal dysfunction differ, and have not yet been fully described.

In type 1 diabetes the most important structural renal changes underlying functional abnormalities occur in the glomeruli [2,3]. The two major early glomerular lesions, mesangial expansion and increased thickness of the glomerular basement membrane (GBM), are not present at diagnosis of diabetes but develop thereafter and can be demonstrated after diabetes has been present for few years [4]. In type 2 diabetic patients, in contrast, several patients, have more advanced tubulo-interstitial and vascular than glomerular lesions [5].

The increase in the proportion of ESRD patients affected by diabetes in the last decades has led to increased research focus on the mechanisms causing renal dysfunction in diabetes and on strategies aimed at preventing, slowing and possibly reversing diabetic nephropathy. Unfortunately, by the time clinical or laboratory abnormalities of diabetic nephropathy become manifest, renal lesions are far advanced [3] and current treatments may slow but usually cannot arrest progression toward end stage renal disease [6–8]. Nevertheless, the natural history of this disease has changed in the last decades.

Clinical trials have demonstrated that improved blood glucose [9–12] and blood pressure control [6–8] slows the development and/or the progression of diabetic nephropathy. Indeed, as a consequence of better metabolic and blood pressure control, especially with renin–angiotensin system (RAS) blockers, the natural history of diabetic nephropathy has changed in the last decades. Thus, it may now be possible to delay or halt the progression toward ESRD in patients with overt diabetic nephropathy [6–8], and to prevent the progression from microalbuminuria to overt diabetic nephropathy [10,12,13]. In the early 1980s the risk of progression to overt proteinuria in microalbuminuric type 1 diabetic patients was estimated to be about 80% over a decade [14–16]. More recently, prospective studies have demonstrated that the percentage of type 1 diabetic patients with microalbuminuria (MA) progressing over 10 years to overt proteinuria is only around 30% [17–21] and a substantial proportion of patients spontaneously regress to normoalbuminuria [17–21].

2. Role of glycemic control in diabetic nephropathy

There is overwhelming evidence indicating that diabetic nephropathy is secondary to the long-term metabolic abnormalities of diabetes.

Glycemic control, as reflected by hemoglobin A1c (HbA1c) levels, has been associated in observational studies with diabetic nephropathy risk [22]. Intensive glycemic control has been shown to decrease the risk to develop early development and delay or prevent progression of diabetic kidney disease. The benefit of intensive glucose control in the prevention of microalbuminuria has been shown in type 1 diabetes by the DCCT trial [9] and in its long term follow-up (EDIC) [10]. The EDIC study also demonstrated a decrease in the risk of proteinuria and of impaired GFR among subjects who were treated intensively early in the course of diabetes [10]. In type 2 diabetes the UKPDS study documented benefit of intensive glucose control in reducing the risk to develop microalbuminuria [11].

The ADVANCE [12] trial more recently confirmed these findings, demonstrating the efficacy of tight glycemic control in reducing the risk of development and progression of diabetic nephropathy. There are no clinical trials addressing the influence of glycemic control in patients with overt nephropathy; nevertheless, current guidelines recommend to keep HbA1c <7% also in these patients.

Glycemic control has a strong impact on the development of renal lesions and renal dysfunction [9–12], as well as on the rate of progression of renal disease [13]. The kidneys of the nondiabetic members of identical twins discordant for type I diabetes were structurally normal, and in each twin pair GBM and mesangial measures were greater in the diabetic twin [23]. Moreover, normal kidneys from nondiabetic donors that are transplanted into diabetic patients develop all of the lesions of diabetic nephropathy [24–26]. Interventions aimed at improving metabolic control clearly influence the development of diabetic nephropathy: type 1 diabetic patients randomized to receive maximized glycemic control, in the first 5 years following kidney transplantation do not develop mesangial matrix expansion, while this occurs in patients randomized to receive standard glycemic control [27]. Finally, the crucial role of glycemic control in diabetic nephropathy is proven by the dramatic reversal of established diabetic nephropathy lesions in the native kidneys of type 1 diabetic patients with long-term (10 years) normoglycemia following successful pancreas transplantation [28] (Fig. 1).

3. Effects of pancreas transplantation on diabetic nephropathy

Pancreas transplantation (PT) offers a unique opportunity to evaluate the impact of prolonged normoglycemia on the different stages of diabetic nephropathy, without exposing the patients to the risks of severe hypoglycemia; thus it has been possible to test the ability of long-term normoglycemia in preventing, halting and reversing diabetic nephropathy. To this end it should be kept in mind that renal functional studies are not adequate for understanding the potential beneficial effects of pancreas transplantation since currently used immunosuppressive agents, especially cyclosporine, have important renal effects, decreasing both glomerular filtration rate and albumin excretion rate. Moreover, abnormalities in renal function usually occur 10–20 years after onset of diabetes and therefore they are impractical parameters to test the