Renal Protection in Diabetes: Role of Glycemic Control

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Diabetes is the most common cause of ESRD in Western countries. This article describes the impact of glycemic control in the various stages of the disease and considers the impact of tight glycemic control on the development and progression of diabetic nephropathy (DN). The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetic Study have demonstrated in type 1 and type 2 diabetes that intensive glycemic control significantly reduces the risk for development of microalbuminuria. Although observational studies suggest an impact of glycemia also on the progression of DN, fewer data are available on the impact of improved metabolic control in secondary prevention. The long-term follow-up of the patients who participated in the Diabetes Control and Complications Trial (Epidemiology of Diabetes Interventions and Complications Study) demonstrated a sustained effect of previous tight glycemic control on both development and progression of DN. Finally, long-term normoglycemia, achieved by pancreas transplantation, is able not only to prevent the development of early diabetic glomerulopathy in kidney transplant recipients but also to halt progression and induce regression of the established diabetic renal lesions in nonuremic patients. Taken together, these studies strongly demonstrate that improvement in glucose control is the most important therapeutic approach in primary prevention. Tight glycemic control also is important in slowing progression of DN, and if blood glucose is normalized, then regression of DN can be achieved. Therefore, a target of glycated hemoglobin levels <7% should be recommended in all patients with diabetes.


Glycemic Control and Development of DN

Epidemiologic studies have demonstrated that DN risk is higher in patients with poor metabolic control (2–5). Although it is clear that genetic factors modulate DN risk and that some patients escape this complication despite decades of poor glycemic control (2–5), it is also clear that hyperglycemia is a necessary precondition for DN lesions and renal functional disturbances to develop. Indeed, the two major early glomerular lesions, glomerular basement membrane (GBM) thickening and mesangial expansion, are not present at diagnosis of diabetes but are found 2 to 5 yr after onset of hyperglycemia (2).

Additional support for the concept that hyperglycemia is necessary for the development of diabetic glomerulopathy is provided by studies in identical twins who are discordant for type 1 diabetes. In these families, the kidneys of the nondiabetic members of the twin pairs were structurally normal, and in each instance, GBM and mesangial measures were greater in the twin who had diabetes in the pair (6). Furthermore, normal kidneys from nondiabetic donors that are transplanted into patients with diabetes develop all of the lesions of DN (7,8).

Finally, patients who had type 1 diabetes and were randomly assigned to receive maximized glycemic control in the first 5 yr after kidney transplantation did not develop mesangial matrix expansion, whereas this occurred in patients who were randomly assigned to receive standard glycemic control (9). This study, along with the very large multicenter Diabetes Control and Complications Trial (DCCT), which documented that patients who were randomly assigned to strict control had lower incidences of microalbuminuria and proteinuria after 7 to 8 yr of follow-up (10), proves the role of glycemia as a risk factor for nephropathy in type 1 diabetes. Similar trends were seen for the prevention of microalbuminuria and proteinuria in the large United Kingdom Prospective Diabetes Study (UKPDS) in patients with type 2 diabetes (11). Perhaps most striking is the dramatic reversal of established DN lesions in the native kidneys of patients with type 1 diabetes and long-term normoglycemia after successful pancreas transplantation (12). Therefore, strategies that aim to improve or normalize the metabolic abnormalities of diabetes could prevent, arrest, or reverse the pathologic influences of diabetes on the kidney.
Glycemic Control and Primary Prevention of DN

The DCCT and the UKPDS have demonstrated in type 1 and type 2 diabetes, that intensive glycemic control significantly reduces the risk for development of microalbuminuria (10,11). In the DCCT, the initially normoalbuminuric patients who were allocated to strict glycemic control had a relative risk reduction of development of microalbuminuria of 34% and of proteinuria of 44% compared with those in the conventional group over 6.5 yr (10). During the DCCT, mean glycated hemoglobin (HbA1c) levels were approximately 7.0 and 9.1% in the intensively and conventionally treated groups, respectively. It is interesting that the benefits of prolonged tight glycemic control persisted also when patients were no longer in intensified glycemic control (13). Indeed, the Epidemiology of Diabetes Interventions and Complications (EDIC) Study (long-term follow-up of the DCCT patients after the end of the study) (13) demonstrated that patients who were on strict glycemic control during the DCCT developed significantly less microalbuminuria than patients who were on conventional treatment after 8 yr from the end of DCCT, with an adjusted risk reduction of 49%, although at similar levels of glycemic control.

In the UKPDS (11), a difference in HbA1c of 0.9% was associated with a reduction in the relative risk for development of microalbuminuria or proteinuria of 30% in the intensively treated group at 9 to 12 yr. Similarly, intensive glucose control reduced the risk for development of microalbuminuria by 62% in a very small number of Japanese patients during 6 yr of follow-up (14). Although it has been proposed that there is a threshold of HbA1c below which DN risk is very low (15), data from the DCCT (16), the UKPDS (17), and the European Diabetes (EURODIAB) study (18) demonstrate that the lower the HbA1c values, the lower the risk for development of nephropathy, with no evidence for a threshold effect. Finally, intensive insulin treatment prevented the development of early glomerulopathy lesions, as elegantly shown in patients who had type 1 diabetes and were randomly assigned to receive maximized glycemic control in the first 5 yr after kidney transplantation, whereas diabetic glomerular lesions developed in patients who were randomly assigned to receive standard glycemic control (9).

In summary, it now is well established that tight metabolic control is effective in achieving nephroprotection in both type 1 and type 2 diabetes and that the lower the HbA1c value obtained, the lower the risk for development of microalbuminuria. No other therapeutic intervention so far has been shown to be as effective as improved metabolic control in the primary prevention of DN in humans.

Pancreas Transplantation and Primary Prevention

Pancreas transplantation (PT) offers a unique opportunity to evaluate the effects of prolonged normoglycemia, without exposing the patients to the risks of severe hypoglycemia; therefore, it has been possible to test the capability of long-term normoglycemia in preventing, halting, and reversing DN. PT most commonly is performed in uremic patients with type 1 diabetes at the time of renal transplantation (simultaneous pancreas-kidney [SPK] transplantation) or, less frequently, shortly after kidney transplant (PAK). SPK offers the opportunity to test the ability of PT to prevent the development of diabetic glomerular lesions, because the renal graft has never been exposed to hyperglycemia. In recipients of SPK (two patients) and PAK (six patients) Bohman et al. (19) first demonstrated that the development of diabetic glomerulopathy was prevented. Glomerular structural parameters still were in the normal range 2 to 8 yr after PT. More recently (20), the same group reported data on a larger cohort of 20 SPK patients who were followed for 1 to 6.5 yr compared with a group of 34 kidney transplant recipients with diabetes, confirming the previous observation.

In addition to the early work of Bohman et al. (19), only one study to date has been performed in PAK patients (21). In this study, PT was performed shortly (1 to 7 yr) after kidney transplantation. Baseline renal biopsies were performed before successful PT and 4 yr later and were compared with those that were obtained at similar times from kidney transplant recipients with diabetes. Mesangial expansion was lower in the recipients of PAK than in the recipients of kidney alone; in contrast, GBM width was not different in the two groups. PAK patients had smaller glomeruli, suggesting that the glomerular enlargement induced by diabetes is reversible. Therefore, PT, performed simultaneously or within a few years after kidney transplant, can prevent or halt progression of diabetic glomerulopathy lesions (19–21).

Glycemic Control and Secondary Prevention of DN

The impact of glycemic control on progression from microalbuminuria to overt nephropathy is less clear (22). In a small study of 26 microalbuminuric patients with type 1 diabetes, during 10 yr of follow-up, progression to overt nephropathy was associated with poor metabolic control (23). The Steno I study (24) demonstrated that 2 yr of strict metabolic control by intensified insulin treatment was effective in reducing progression to overt nephropathy in microalbuminuric patients with type 1 diabetes. In the DCCT, there was no difference in the number of patients who progressed from microalbuminuria to overt nephropathy between the intensively and conventionally treated patients (25); it should be kept in mind, however, that at the end of the DCCT, only 10 of the 73 originally microalbuminuric patients had progressed to proteinuria (25). The beneficial effects of tight glycemic control, in contrast, clearly emerged during the subsequent 8 yr (EDIC Study); indeed, despite no difference in metabolic control between groups, patients who were treated intensively during DCCT had a risk reduction to progress to proteinuria of 84% compared with conventionally treated patients (13). These findings suggest that previous intensive treatment with near normoglycemia during DCCT had an extended benefit in slowing progression of DN. The UKPDS (11) did not report data on the impact of intensive glucose control on the progression from microalbuminuria to overt nephropathy; however, during the 15 yr of the study, there was a beneficial effect on both development of proteinuria and doubling of serum creatinine (11). The Kum-
amot study, in a small number of microalbuminuric patients with type 2 diabetes, reported a significant reduction in progression to proteinuria in patients who were on an intensive insulin regimen (26). The effects of improved metabolic control on glomerular structure have been tested by sequential kidney biopsies in a small group of patients with type 1 diabetes and microalbuminuria (27). In this study, nine patients received intensive insulin therapy and nine received conventional treatment. At the end of follow-up (24 to 36 mo), diabetic glomerulopathy lesions progressed less in the intensively treated group than in the conventionally treated group (27).

In patients with overt nephropathy, observational studies have demonstrated the influence of metabolic control on the rate of progression of DN is not supported by large and long-term intervention studies.

Pancreas Transplantation and Secondary Prevention

In patients with diabetes, the possibility to halt or reverse DN lesions can be addressed adequately by studying the recipients of PT alone (PTA). We studied 13 PTA recipients and found that, despite 5 yr of normoglycemia, there was no amelioration or reversal of the established DN lesions (30).

Of the original cohort of 13 PTA recipients, eight were available for studies after 10 yr of normoglycemia (12). The data on renal function in these patients are complex to interpret, given the effects of cyclosporine on GFR and albuminuria. As far as renal structure is concerned, there was no beneficial effect on glomerular structure at 5 yr after PTA; in contrast, we observed obvious reversal of diabetic glomerulopathy lesions in all eight patients, with glomerular and tubular morphometric parameters returning to the normal range in several instances. GBM and tubular basement membrane width, unchanged at 5 yr, decreased at 10 yr of follow-up. The values at 10 yr fell into the normal range in several patients and in the remaining patients were approaching normal. Mesangial fractional volume and mesangial matrix fractional volume increased from baseline to 5 yr but were lower at 10 yr than at baseline or 5 yr. Light microscopic observations revealed a remarkable remodeling of glomerular architecture in these patients, including the total disappearance of Kimmelstiel-Wilson nodular lesions and reopening of glomerular capillaries that previously were compressed by mesangial expansion. Therefore, this study provides clear evidence that diabetic glomerular and tubular lesions are reversible in humans (12).

The reasons for the long delay in reversal of DN lesions are unknown. It can be hypothesized that renal cells have developed “memory” for the diabetic state (31) or that extracellular matrix (ECM) molecules are heavily glycosylated and therefore more resistant to proteolysis until replaced by less glycosylated molecules (32). Nevertheless, the long time necessary for these diabetic lesions to disappear is consistent with their slow development. In fact, diabetic renal lesions develop and progress from onset of diabetes during at least 1 decade before they can cause any functional abnormality (2). Regardless of the mechanisms involved, at some point after PTA, ECM removal begins to exceed ECM production. This is abnormal because, normally, renal ECM production and removal remain in near perfect balance during adult life. If normal balance had been reestablished, then the renal lesions would have remained stable, but this was not the case. In simplest terms, glomerular and tubular cells can “sense” that their ECM environment is abnormal and can alter their behavior toward ECM removal and architectural remodeling. Therefore, these studies indicate that diabetic renal lesions are not only preventable but also reversible. Despite these encouraging results, however, PT cannot be considered a primary treatment for DN. It is possible, however, that this view will change in the near future with the development of nonnephrotoxic immunosuppressive agents and with better outcomes of islet transplantation.

In summary, glycemic control significantly influences the rate of progression from microalbuminuria to proteinuria and from overt nephropathy to ESRD. Although large and long-term randomized trials on the effect of improved metabolic control on progression of DN are lacking, results from PT recipients and the EDIC study support the concept that very prolonged periods of extremely good metabolic control are necessary to have a positive impact on progression or even obtain regression of DN. Therefore, according to current guidelines (33), a target of HbA1c level of <7% is recommended in all patients with diabetes to preserve their kidney function.

References


