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**De novo diabetes in dialysis patients: when diabetes is not diabetic nephropathy**

C. Catalano

Centro di Fisiologia Clinica del Consiglio Nazionale delle Ricerche, Reggio Calabria, Italy

**Key words:** diabetes mellitus, non-diabetic nephropathies, *de novo* diabetes during dialysis, end-stage renal disease

**Introduction**

In patients with renal failure, the presence of diabetes has nearly always been equated with the presence of diabetic nephropathy. However, in real life the situation is more complex.

Figure 1 shows the possible pathogenetic relationships between diabetes and renal disease. The first possibility is that diabetes causes renal disease (diabetic nephropathy). Alternatively, renal disease may directly or indirectly cause diabetes. Finally, no cause-effect relationship may be present, in which case diabetes and kidney disease coexist independently in the same patient.

As far as the temporal relation between diabetes and kidney disease is concerned two situations may exist; first, the diagnosis of diabetes may precede the diagnosis of renal disease; second, the diagnosis of renal disease may precede the diagnosis of diabetes. In the first instance renal disease may or may not be secondary to diabetic nephropathy. In the second case (*de novo*) diabetes may or may not be related (directly or indirectly) to the nephropathy or to nephropathy treatment.

In this comment, I will focus on the topic of *de novo* diabetes in uraemic patients trying to review both the magnitude of the problem, the mechanisms potentially involved, and the consequences of diabetes on survival of RRT patients.

**Dimensions of the problem**

Post-transplantation diabetes mellitus is frequent, affecting 10–20% of transplanted patients [1], and it is considered to be secondary to the action of steroids (which impair non-oxidative glucose disposal) and cyclosporin A (which induces insulin resistance and decreases insulin secretion). Recently it has been shown that post-transplantation diabetes mellitus is potentially reversible after steroid withdrawal in selected cases [2].

Whilst post-transplantation diabetes mellitus has raised the attention of clinicians and researchers, there...
is very little information on the issue of de novo diabetes mellitus in maintenance dialysis.

It has been reported that severe hyperglycaemia in dialysis patients treated by dialysis may be asymptomatic [3]. It has been suggested that the absence of osmotic diuresis and the lack of substantial osmotic ultrafiltration may prevent the development of hypernatraemia and marked hyperosmolarity [3]. Moreover, it is documented that metabolic acidosis in diabetic dialysis patients is very rare [4]. However, missing the diagnosis of diabetes in dialysis must be rare because of the frequent blood testing together with the widespread use of multianalysers.

Kurtz et al. in 1983 reported that three of 40 (7.5%) non-diabetic CAPD (continuous ambulatory peritoneal dialysis) patients required insulin administered intraperitoneally in order to control plasma glucose levels [5]. Gonzales et al. in 1985 reported that three of 47 diabetic patients (6.4%) treated in the Avram Center for kidney diseases, had diabetes diagnosed after dialysis was started [6]. Lindholm and Bergström reported de novo diabetes mellitus in five of 95 (5.3%) non-diabetic CAPD patients [7]. A similar proportion (6/60 of diabetic dialysis patients) was found by our group in a preliminary survey of diabetic patients on regular haemodialysis. In 1988 we reviewed this issue in overall Italy [8]. In 79/1605 diabetic patients (4.9%) diabetes was reported to have been diagnosed on average 8 years after the diagnosis of chronic renal failure, and in 44/1605 diabetic patients (2.7%), diabetes was reported to have been diagnosed after the start of RRT. Eight of those had a history of kidney transplantation. Two patients were on treatment with CAPD when diabetes was diagnosed, whilst the other 34 were treated by haemodialysis. If we consider that in the period 1983–87, around 25 000 non-diabetic patients were being treated by RRT in Italy (data courtesy of ANED Registry), we may calculate that the prevalence of de novo diabetes in the RRT population was roughly in the range of 0.15–0.20%.

Mechanisms associated with the emergence of diabetes in patients with chronic renal failure

First of all it is possible that the diagnosis of de novo diabetes is incorrect, because the patient was already diabetic but the disease had not been diagnosed (Pseudo de novo diabetes). Diabetes may become apparent during the course of chronic renal failure because of weight loss and increased half-life of insulin. In such patients the disease may reappear again once the nutritional condition improves and especially if the patient is loaded daily with glucose during peritoneal dialysis. On the other hand, de novo diabetes may represent the natural evolution of a disease that would have emerged anyway. This possibility arises particularly because of the fact that both the incidences of diabetes and renal failure increase with old age. Another possibility is that diabetes is a consequence of the autoimmune mechanism responsible for the primary nephropathy. IDDM is caused by autoimmune damage of pancreatic islets and most primary or rapidly progressive glomerulonephritides are caused by immune mechanisms. However, antigens and mechanisms are different, and I am not aware of any report concerning a specific association between these two groups of diseases. Finally, in chronic dialysis many factors may interfere with both insulin sensitivity and/or insulin secretion, causing the emergence of diabetes. Since many factors may be involved, we will try here to explore these possibilities in greater detail (Table 1).

Patients with rapidly progressive nephritis are usually treated by immunosuppressive drugs and steroids. If renal function declines quickly, then this subset of
patients may develop diabetes in coincidence or soon after the start of dialysis. Other drugs are known to interfere with insulin secretion or insulin sensitivity: beta-blockers impair glucose tolerance and can occasionally cause hyperglycaemia. On the other hand, carbohydate tolerance is improved by ACE inhibitors in some patients.

Especially in the pre-erythropoietin (Epo) era, a high proportion of RRT patients suffered from secondary haemochromatosis which may cause diabetes [9], and iron overload has been associated to insulin resistance [10]. However, I am not aware of any case reported concerning haemochromatosis-related diabetes in RRT, even if I remember a young female patient with very high ferritin levels who developed insulin-requiring diabetes immediately after a kidney transplant (unpublished data).

There are some data suggesting that Epo treatment may interfere per se with glucose tolerance in dialysis patients, but results are controversial [11,12].

Exchanges with isotonic dialysate in patients on peritoneal dialysis (PD) have only a marginal effect on blood glucose and insulin levels. However, in these patients there is a tendency toward hyperglycaemia and consequent hyperinsulinaemia [13]. It is known that sustained, physiological elevation of the plasma glucose concentration leads to an impairment in insulin secretion (so-called glucose toxicity). There are at least two reports concerning de novo diabetes in CAPD patients [5,7] whilst other researchers have observed non-insulin-dependent patients in CAPD, becoming insulin requiring [14]. On the other hand, only a minority (2 of 36) of the Italian patients with de novo diabetes were treated by PD when diabetes was diagnosed.

It is known that uraemic patients are insulin resistant and that insulin resistance abates after dialysis is started. To my knowledge, however, no follow-up data is available; it is possible that in patients on maintenance dialysis, the sensitivity to insulin decreases over the years together with the development of arteriosclerosis. This issue, however, is very difficult to address because the factors involved in the genesis of glucose intolerance in uraemic patients on treatment are countless and are susceptible to change through the years.

Awareness of the clinical importance of nutritional problems in uraemic patients is now widespread among nephrologists. Often the patients are malnourished, and it has been suggested that there exists a malnutrition-related diabetes mellitus (MRDM). In this respect, it is interesting to remember that in the past, chronic renal failure had been associated with diseases of the exocrine pancreas [15]. On the other hand, Lindholm and Bergström have observed that their patients who developed de novo diabetes whilst on CAPD had markedly increased body weight [7] and they suggested that in those patients, diabetes may be related to increased peritoneal absorption of glucose and consequent excess caloric intake and glucose toxicity.

Deposition of islet amyloid polypeptide (IAPP) in the pancreatic islets is a characteristic feature of non-insulin-dependent diabetes, and it has been shown that amylin is toxic to beta-cells in NIDDM [16]. A recent paper has highlighted that 35% of non-diabetic patients on haemodialysis present islet amyloid deposits compared to only 3% of non-diabetic, non-uraemic controls [17]. It cannot be excluded that this deposition might interfere with insulin secretion in uraemic patients.

Plasma triglycerides levels are associated with insulin resistance and there is evidence that in patients on chronic dialysis, hypertriglyceridaemia may develop or worsen, especially in patients on chronic peritoneal dialysis.

Finally, there is evidence that hyperparathyroidism (a frequent condition in patients with chronic renal failure) interferes with the ability of the β-cells to augment insulin secretion appropriately in response to the insulin-resistant state [18].

**Consequences of de novo diabetes on patient survival and on patient management**

In a matched-pair control study, Von Kiparski et al., demonstrated that in the long term post-transplantation diabetes mellitus affects both patient and graft survival [19]. Similarly, we have data showing that after 4 years follow-up, the survival of 34 de novo diabetic patients on RRT was worse compared to a control group and not improved compared to a group of patients with a primary diagnosis of diabetic nephropathy [20].

A poor outcome in the de novo diabetic patients within a relatively short follow-up is somehow unexpected and it is difficult to find a satisfactory explanation for this finding. We may hypothesize that this unfavourable outcome might be related to the presence of factors causing both diabetes and systemic damage (e.g. related to the metabolic syndrome), or alternatively related to the emergence of an additional risk factors in already compromised patients. In this respect, the potential hazards of glucose intolerance in uraemics have been previously discussed in detail by DeFronzo and Smith [21].

It is beyond question that confirmation of available data and further studies are necessary. However, these data seem to show that treatment of diabetes and associated risk factors has to be equally aggressive in
RRT irrespective of the primary renal diagnosis and of the apparent duration of the diabetic disease.

Conclusions

Available data suggest that a proportion of RRT patients develop diabetes after renal treatment is started. The pathogenesis of the disease is multifactorial. In any case diabetes has a strong impact on survival. I hope that this editorial comment may motivate other nephrologists to review and report their own data concerning the emergence of diabetes in dialysis patients, since currently information in this field is woefully incomplete.

References


Editor's Note

Please see also the Brief Report by Catalano and Postorino (pp. 1124-1128 in this issue).

Are cardiac troponins reliable serodiagnostic markers of cardiac ischaemia in end-stage renal disease?

C. Haller, A. Stevanovich and H. A. Katus

Department of Internal Medicine III, University of Heidelberg, Heidelberg, Germany

Introduction

In classical cases the effective management of massive acute myocardial infarction can be based exclusively on typical changes in the ECG in order to obtain the maximum benefit from timely reperfusion. In the real world, however, a clear-cut diagnosis from the ECG is often not possible, at least not initially, so that additional diagnostic tests are necessary to arrive at a definite diagnosis early on. In this setting the conventional cardiac enzyme assays have limitations not only because serial measurements over several hours may be required, but also because they lack sufficient

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