See original article on page 626

The treatment of diabetic patients on peritoneal dialysis remains a challenge 25 years later

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RELEVANCE OF DIABETES MELLITUS IN NEPHROLOGY

Diabetes mellitus (*DM*) is the most important disease related to renal replacement therapy (RRT), due to its prevalence and clinical, economic and social impact. It is estimated that 0.3% of the general population suffer from type 1 *DM* and 7% from *DM* type 2.[1] The prevalence of *DM* is dependent on the diagnostic criteria used and varies throughout the world, but the increase in the incidence of type 2 *DM* is estimated between 3 and 5% annually.[1] This is due largely to poor health habits; therefore, its growth is even higher in developing countries. Progression to chronic kidney disease (CKD) in stage 5D increases due to a more prolonged exposure to hyperglycaemia, its association with high blood pressure (HTN), obesity, sedentary lifestyle and other risk factors, and its lower mortality, which leads to patients undergoing RRT. Therefore, the term "epidemic of the 21st century" is no exaggeration.

It is estimated that the overall cost of treating patients with type 2 diabetes with target organ damage is at least €2,136 per year and may exceed €54,000 per year for patients on haemodialysis (HD). Finally, *DM* is a cardiovascular (CV) risk factor and a source of clinical complications, hospital admissions, poor quality of life and loss of years in full health and at work. This disease has a significant impact.

Data from monitoring more than 5,000 patients in the UKPDS study allowed us to establish the clinical course of nephropathy in type 2 *diabetes mellitus*.[2] Statistically, it takes 19 years to develop the disease, 11 years to go from microalbuminuria to macroalbuminuria and a decline in renal function starts 10 years later. However, patients who were included in the UKPDS with a Cr greater than 2mg/dl were undergoing RRT in just 2 years, which is the patient profile faced regularly. The objective of intervention in *DM* is clearly in the initial stages, focusing on renoprotection and cardioprotection, reducing CV events and the need for RRT. In fact, there is now evidence that intervention and close monitoring of patients with type 1 diabetes reduces the need for RRT in these patients. A Finnish study of 20,000 patients followed between 1965 and 1999, had dialyisis incidence rates of only 2.2% aftet 20 years, and a trend to decrease in the more recent years.[3]

Nevertheless, the challenge of treating *DM* patients on dialysis is an ongoing one. Articles like the one presented in this issue by the group from the Hospital Universitario San Carlos, Madrid, gives a historical perspective on the treatment of diabetic patients on peritoneal dialysis (PD[4]).

There are not many PD programmes with a experience of 25 years, as in this study. The most relevant result is the description of a worse outcome for patients with *DM* and the quantification of this risk in our area.[4] Patients with *DM* in this study have higher rates of mortality, transfer to HD, hospital admissions, non-peritoneal infections and peritonitis, in line with previous published studies.[5] For example, in the study of the *Grupo Centro de Diálisis Peritoneal, GCDP* (Peritoneal Dialysis Group Centre), the probability of survival at 2 years was 86.7% in patients without *DM* and 75.2% in patients with type 2 *DM*.[6] In the study published in this issue, however, two different historical PD periods were compared. The most recent

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(post-1992) had double-bag systems, the first glucose-free solutions and the widespread use of automated systems, as well as erythropoietin. In this second phase, the rate of peritonitis was reduced accordingly and global outcome indicators improved, although the risk of death attributable to *DM* was not significantly reduced.

The first stage of the article referred back to the 1980s (pre-1992), when some groups raised concerns about the appropriateness of including patients with *DM* in dialysis programmes due to its high morbidity and mortality. This period (pre-1992) has some striking data reflecting a negative selection of patients for PD, which was not specifically outlined in the article. For example, the prevalence of diabetic patients on PD was 55% compared to the average reported by the register of 18% on HD, or 20% recorded by the *GCDP* between 2003 and 2009.[5] In addition, they reported a high percentage of patients with blindness and other comorbidities, which limited the number of patients stopping the therapy to undergo transplant surgery to only 5.8% in the total follow-up of patients with type 2 *DM*. The low HD transfer rate could be due to the previous technique being maintained well or because patients were not able to change from one technique to another. In other words, it would be patients indicated for PD rather than those choosing PD, which is a risk factor in itself.[7]

Against this backdrop, the "new" integrated RRT 3.0 model offers an integrated approach for dialysis techniques and transplantation with a fluid exchange between them, as each reaches a plateau in a particular patient.[8] This model is becoming a reality in many Spanish hospitals.

The study published by Coronel et al. also serves as a reference for comparison for other groups starting PD. In general, these PD programmes are not large. For example, the Community of Madrid has an average size of around 25 patients, with a high turnover, fluctuations in the number and difficulties with growth. Therefore, retrospective studies of this type have been used so far as a reference to reflect the reality of PD in our area and time, highlighting differences with studies in other health systems and other countries. The collaboration between institutions is necessary to begin to have benchmarks for comparison with recent larger multicentre data.[9]

DM is the most important risk factor for PD patients and this poor prognosis is related to the CV pathology of patients entering PD, as indicated by other studies.[6] The study by Coronel et al. shows an overall risk of death from *DM* of 1.96 compared to non-*DM* patients on PD. Although they did not have their own data on the evolution of *DM* patients on HD, as it was not the objective of the study, the comparison between techniques is inevitable. External references show a similar picture on the evolution of *DM* patients on HD. According to the 2009 USRDS report, only 30% of *DM* patients survive 5 years after starting HD, and these data would be even worse if the early mortality of patients who did not reach 3 months in HD were included (excluded from that register[10]).

The paper reports that half of the deaths were associated with CV events. The morbidity of *DM* is associated with predialysis CV damage, the concomitance of other risk factors (dyslipidaemia, HTN, etc.) and tissue deposition of advanced glycation end products (AGE). AGEs that accumulate in CKD have a direct effect on the vascular wall, promoting accelerated atherosclerosis and protein-calorie malnutrition. In fact, in some series, the risk attributable to *DM* greatly diminishes if corrected for the presence of previous cardiovascular events and albumin levels.[11] For example, the data presented by the *GCDP* indicate that the risk of death in type 2 diabetes patients is 2.5 times that of non-*DM* after correction for age. The association between type 2 diabetes and previous cardiovascular events excludes the variable type 2 *DM* due to trying to put it in the same model *DM* and CV event prior to PD.[6,7]

The comparison of survival between HD and PD remains controversial, especially because the information comes from records and observational studies or from post-hoc analyses. Such questions cannot be resolved with a clinical trial design, so the information must come from observational studies with a prospective design and sufficient sample size and control of covariates and confounding factors. A recent comprehensive review in our journal concluded that both techniques were similar, with a slight advantage for PD in the first 2-3 years of evolution and HD later. In the specific case of patients with *DM*, younger people seem to have better outcomes with PD and the elderly with HD.[12]

A recent retrospective study goes beyond the multivariate analysis using the propensity score to reduce the selection bias of either technique.[13] This study gives an advantage to patients on PD, particularly in the initial period, with a probability of survival of 85.5% compared with 80.7% in HD, and 71.1% versus 68% in HD after 2 years ($P<.01$), the trend continues without reaching significance in the third year. Overall, the risk of death favours PD by 8% in the ITT analysis. However, in the stratified analysis for diabetic patients, this benefit was only seen in the first year. The authors conclude that PD may be a good initial RRT technique. This advantage of PD in the early stages may be related to the better preservation of residual renal function and worse outcomes after a while, with the failure to control the volume or metabolic factors.

In short, PD as a technique appears to be at least as good as HD for RRT patients, therefore patient choice must be considered in the decision-making process in most cases.

WHAT ARE THE THEORETICAL ADVANTAGES AND DISADVANTAGES OF PERITONEAL DIALYSIS FOR *DIABETES MELLITUS* PATIENTS?

PD has a number of theoretical advantages for patients with *DM*, such as better haemodynamic tolerance, maintenance of residual renal function, vascular capital preservation and use of peritoneal insulin for improved glycaemic control (currently not used). HD currently has a less stable electrolyte profile associated with a greater incidence of arrhythmias, the high-flow prosthetic fistulas lead to a haemodynamic overload which, along with hypertension, promote the development of left ventricular hypertrophy (LVH). These factors are behind the episodes of sudden death in HD. On the other hand, patients with *DM* have specific risks with this technique, primarily metabolic. Diabetic gastroparesis worsens in PD and promotes anorexia and secondary malnutrition. Glucose overload increases insulin resistance and makes it difficult to control the lipid profile.

Diabetic patients have a thicker, poorly vascularised peritoneal membrane even before starting PD, as demonstrated in peritoneal biopsies obtained after inserting the catheter.[14] This may influence the poorer outcome in peritoneal permeability in the medium term.

INTEGRATION VIA THE RRT 3.0 MODEL FOR *DIABETES MELLITUS* PATIENTS

We can summarise that PD seems to be a good starting technique for RRT with *DM* patients and has a certain advantage in the first 2 years. The current concept considers RRT as an integrated service of PD, HD and transplant (TX[15]). There is no evidence to guide our *DM* patients towards one particular technique or another, and key factors such as comorbidity, social situation and, above all, patient preference should be a starting point for RRT.

In fact, the model proposed by some groups suggests the use of PD initially, and early TX, while keeping HD for those patients where PD fails.[16] Early TX is the best alternative for patients with *DM* whose comorbidity does not prevent it. The US renal registry has a survival rate for *DM* undergoing TX of 67%-77% at 5 years.[10] Although still lower than that of non-*DM*, it is a significant improvement on the 30% survival at 5 years for *DM* patients treated with HD or PD. It may be that recovering renal function promotes the elimination of AGEs from *DM* and other uraemic mediators that favour accelerated atherosclerosis and are agents of direct vascular injury. In addition, TX is associated with a better quality of life and rehabilitation, personally and at work. Therefore, TX should be offered to all diabetic patients in RRT without absolute contraindication and as early as possible.

FUTURE MANAGEMENT OF *DIABETES MELLITUS* IN RENAL REPLACEMENT THERAPY

Another worth noting part of the study presented in this issue is that the prognosis of patients with type 2 diabetes does not improve in the second stage (post-1992). Despite technical advances in the treatment: double bag, cyclers, use of erythropoietic agents and the new drugs at our disposal for controlling blood pressure, dyslipidaemia, glycaemia and mineral vascular disease, the mortality is unchanged. It is true that hospital admission rate and annual stay in the most recent period are reduced, but we do not know if it is as a result of a better prognosis or overall improvement in hospital ambulatory processes and reduced stays. Although the authors have not given a detailed analysis of comorbidity between both stages, non-*DM* and *DM* type 1 patients who began PD after 1992 have improved their prognosis.

Many misleading factors may interfere with an analysis like this, because other studies have reported an overall improvement in results over the years. For example, in the US registry, the mortality of diabetic patients on HD and PD was reduced from 27.4% in 1980 to 18.6% in 2007 and *DM* survival after PD improved by 21.8% in the last half of the 1990s.[10] Other studies in the same country showed a lower peritoneal technique failure rate when comparing the 2002-2003 period with the 1996-1997 period.[17] Although we have no data published by the Spanish registry for patients with *DM*, global annual mortality improved from 12% in PD in 2002 to 7.8% per annum 5 years later.[18]

The treatment of *DM* patients on PD requires dedication and integrated monitoring to reduce cardiovascular risk on all fronts. Diet, exercise and weight control are crucial, as well as control of fluid intake, which reduces the use of hypertonic solutions. A new indication for glucose-free solutions was discovered with icodextrin or amino acids as agents to reduce glucose intake for patients. In addition, the importance of preserving RRF makes all the kidney protecting measures in the pre-dialysis stage continue to have an effect. We have no evidence that glycaemic control, the use of RAAS blockers or other measures reduce the mortality of our patients. We sincerely think it is difficult to implement a randomised trial with mortality targets to test these intervention measures at present, but there is a whole pathophysiological substrate and partial evidence indicating that the hope of maintaining FRR and improving survival of *DM* on PD is on the right path.[19]

Until recently, it was accepted that diabetic patients should start dialysis early, even earlier than non-*DM* patients. However, the IDEAL study released this year, which is a randomised clinical trial of 828 patients followed over three and a half years, shows no benefit in starting scheduled RRT at a clearance between 10 and 14ml/min compared to doing so at 7ml/min.[20] It must be made clear

that the study allowed patients with symptoms or without complications to start RRT. In fact, 76% of patients assigned to a late start did so before reaching 7ml/min renal function. Finally, there was only 6 months difference between the start of RRT in the two groups. The survey is not specifically dedicated to patients with *DM* or PD, but provides evidence for inclusion in RRT after a patient's complete clinical assessment and against early initiation strategy based solely on figures. In any case, PD has the added advantage of allowing a gradual start relying on and caring for RRF. Recently, it was seen that patients with preserved RRF have less vascular calcification and that this factor could be involved in the protection of that residual diuresis.[21]

The future of PD for patients with *DM* is via peritoneal membrane protection, minimising glucose load, using new, more biocompatible solutions, preventing peritoneal infections and developing specific treatments to prevent peritoneal fibrosis.

While we await the results of early intervention on cardiac and renal damage in our patients, we must strive to improve the prognosis of diabetic patients reaching RRT. PD appears to be a better starting technique than HD for those patients who choose it, due to its lower mortality in the first 2-3 years, greater independence and improved efficiency, because of its lower cost. At that time, we should be able to provide the patient with TX. If this is not possible, integrated control must be maintained according to Table 1 with RRF protected. Once PD is insufficient to maintain the patient's situation, we must offer the transfer to HD within an integrated model.

Table 1. Measures to improve long-term outcomes in diabetic patients on peritoneal dialysisl

Preserve peritoneal membrane:
• Prevent peritonitis (periodic training and, after peritonitis, attention to carer fatigue, prophylaxis of orifice infection)
• Reduce use of hyperosmolar and bioincompatible solutions
• Progressive dialysis to keep a dry day if possible
Improve glycaemic control:
• Reduce glucose load in solutions (icodextrin, amino acids)
• Appropriate use of insulin profiles
Control of cardiovascular risk factors specific to CKD-PD:
• Avoid cardiac overload due to excess hydration (diet, diuretics)
• Regulated monitoring of cardiac function
• Reduce inflammation (if CRP high → study possible causes)
• Correct 25-OH-vitamin D deficit
• Correct hyperphosphataemia
Control cardiovascular risk factors:
• Hypertension
• Obesity
• Dyslipidaemia
• Smoking
Elective transfer to HD when needed. Integrated RRT

Modified from reference 22.

KEY CONCEPTS

1. DM determines a poor prognosis in any dialysis technique mainly at the expense of added CV damage.
2. The future is early detection and intervention with kidney protection measures.
3. PD results have improved in recent years.
4. PD is a good starting technique for RRT in DM patients. Transplant is the technique of choice and should be performed as early as possible.
5. The RRT integrated model is the only technique recommended that maintains free choice and is economically sustainable.

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