Is Glucose a Problem in the Dialysate for Diabetic PD Patients?

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Diabetes is commonly present in the patients with end-stage renal disease (ESRD) requiring regular renal replacement therapy. In continuous ambulatory peritoneal dialysis (CAPD) patients, supraphysiological concentration of dextrose has been widely used as dialysate in the peritoneal dialysis (PD) fluid for the past two decades. Depending on the period of exposure and the strength of the dextrose solution used, 320-700 KCalories of additional energy daily intake may result from peritoneal dialysis. Not surprisingly, this has caused some concern, not least due to the direct glucose toxicity to the peritoneum membrane but also the possible adverse metabolic consequences, such as obesity, increased insulin resistance and dyslipidaemia. However, is this concern regarding metabolic effect as a result of dextrose dialysate justified?

Body mass index & mortality in ESRD patients

Malnourishment as reflected by low BMI has been linked with increased mortality in patients with ESRD. Numerous studies have shown that patients undergoing chronic peritoneal dialysis do not have adequate dietary protein and energy intake. For instance, Wang and colleagues studied nutritional intake in 266 ESRD patients (31% had diabetes) and found that 75% of patients had energy intake <126kJ/kg/day. Even with the addition of peritoneal glucose intake, only 20% of patients achieved the recommended intake of 146 kJ/kg/day. In another study, Jacob et al found that in 61 CAPD patients, over 63% had inadequate energy intake, as assessed by a low triceps skinfold thickness or a reduced midarm muscle circumference. Hence additional calories from glucose through PD fluid could potentially be beneficial if appropriate therapy is given to maintain euglycaemia in those with diabetes.

The concern about possible weight gain as a result of chronic PD therapy is not well established. Studies from Korea, Sweden and America have shown that PD patients have either normal or only slightly high BMI. In these studies, data on waist circumference (marker of visceral obesity) were not provided. On the other hand, data from large-scale studies showed a trend towards “reverse epidemiology” with regard to obesity and mortality in ESRD patients. Whether this is a true phenomenon remains a subject of debate. Meanwhile, there is no clear evidence that obesity (as reflected by increased BMI) confers extra risks in PD patients. It is very likely that it is the loss of lean muscle weight (as a result of malnutrition) which determines the short-term mortality in ESRD patients and these patients do not survive long enough for high BMI to have an impact.

Does dextrose dialysate worsen glycaemic control?

The claim that dextrose dialysate worsens insulin resistance is also unproven. Szeto and colleagues studied a cohort of 60 Chinese insulin-treated diabetic patients who have just been started on PD therapy. They found that slightly increased subcutaneous insulin (0.103 unit/kg/day) was required over a period of 6 months; there was no change in glycaemic control. This increase in insulin was mainly confined to patients on higher dextrose dialysate concentration. There was no evidence that extra glucose loading from PD leads to deterioration in glycaemic control if insulin therapy is appropriately titrated. Given that ESRD patients with diabetes are often insulin resistant, the use of insulin sensitisers such as thiazolidinedione therapy in diabetic PD patients may have a role. Another study of Chinese diabetic patients by the same research group examined this issue. Fifty-two insulin-treated diabetic patients were randomised to receive either add-on rosiglitazone therapy or remained on insulin alone. After 24 weeks, total insulin dosage was significantly decreased in the rosiglitazone group compared to the control group (-21.5% vs +0.5%). Furthermore, the rosiglitazone therapy was associated with significant reduction in C-reactive protein. These results are certainly promising but long-term outcome studies would be required. While glycaemic control is important in preventing micro- and macrovascular complications, in ESRD patients, it has been shown that pre-dialysis glycaemic control is an important determinant of mortality. Intra-peritoneal insulin therapy has been advocated by some nephrologists in the past which was thought to be more physiological. Literature on the comparison between peritoneal insulin and subcutaneous insulin has been sparse. Torun and co-investigators compared the use of peritoneal insulin and subcutaneous insulin in a small
number (n=14) of diabetic patients. They found that when compared with subcutaneous insulin, intra-peritoneal insulin was associated with significantly greater weight gain, higher triglyceride levels, higher glucose load in dialysate and higher insulin dosage. Furthermore, 5 out of the 8 patients on intraperitoneal insulin developed hepatic subcapsular steatosis10. Currently, most centres are using subcutaneous rather than intraperitoneal insulin. The impact of diabetes education should be emphasised as it has been shown to improve glycaemic control and patient outcomes in ESRD patients11 just like those without chronic kidney disease.

Dyslipidaemia and glucose loading

Worsening of dyslipidaemia occurs in PD patients with a gradual rise in triglyceride and total cholesterol12,13. Several studies have considered glucose loading in PD fluid as a contributory factor but results have been conflicting. In a retrospective study of 102 CAPD patients, Olivaries et al found an initial rise in serum triglycerides related to glucose load which was not sustained and began to normalise after 2 years of CAPD14. In another study, Little et al found that in a prospective cohort of 124 ESRD patients, serum triglyceride and total cholesterol were elevated after PD when compared to baseline but more so in the group with pre-existent cardiovascular disease15. This is most likely to be due to a genetic predisposition in this group of patients. In this study, the strongest predictor of worsening of dyslipidaemia was weight gain and was not associated with glucose loading15. Similarly, a study of 22 non-diabetic PD patients from Sweden also confirmed the lack of effect of PD glucose loading on worsening of dyslipidaemia16.

Summary

In summary, dextrose dialysate fluid has not been shown to result in derangement in metabolic parameters. Alternative dialysate fluids such as icodextrin and amino acid PD fluids have been developed which are generally more expensive and have their own limitations. Good glycaemic control pre-dialysis is paramount in reducing mortality in diabetic PD patients. Well-designed large-scale outcome studies are required to determine the most appropriate PD fluid for diabetic ESRD patients.

References


PD First Strategy for Diabetic Patients

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Until some years ago, each renal replacement therapy (RRT) was considered as a separate entity, an approach that neglected completely the fact that most patients transfer between the different modalities over time. The concept of integrated care (figure) aims at providing the most optimal therapy at each time of the disease process for each patient1. The question is thus not "which treatment is best" but "which succession of treatments will give the best outcome in the long term". Also for diabetics, this integrated care concept makes sense, and presenting PD as a very good starting modality for RRT should be encouraged.

The Integrated Care Model

PD as a first line therapy

Outcome on PD in diabetics

The first question when advocating a RRT modality is of course whether this choice would impact on the survival of the patient.
Survival analysis of PD vs haemodialysis (HD) shows a different picture in the US as compared to Europe and Asia. In European studies, almost all report a survival benefit or a comparable survival on HD vs PD in diabetic patients, especially in the first 3-4 years of the treatment.

The data of the USRDS database seem to indicate that mortality is lower in PD vs HD in younger diabetics, but worse in older diabetics, especially if they are female. This interpretation can be seriously questioned because of different reasons. First, the USRDS database only includes patients after 90 days, favouring the “worst” modality by selecting only the fittest patients. Second, the patient numbers in USRDS are very high, making that statistically significant does not equal clinical significance. This was neatly shown by Vonesh et al., who found alternating superiority of HD and PD in consecutive and overlapping cohorts of USRDS. Third, both the approach to PD as the patient mix is quite different in the US as compared to the rest of the world. It is thus well accepted these days that well performed PD results in an at least as good outcome as HD also in diabetic patients.

**Advantages of PD first in diabetic patients**

There are several reasons why PD should be a good option to start RRT in diabetic patients (table 1).

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<th>Table 1: factors in favour of PD as a first line treatment</th>
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<td>Vascular access</td>
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<td>Residual renal function</td>
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<td>Cardiovascular mortality</td>
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<td>Infectious (Viral) contamination</td>
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<td>Outcome after transplantation</td>
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<td>Cost/benefit</td>
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The most prominent advantage is the lack of need for vascular access. It is well established that the creation of vascular access can be quite cumbersome in diabetic patients, especially when they are older or female or have cardiovascular comorbidity. In DOPPS for example, diabetics were 25% less likely to be dialysed with a native fistula than non-diabetics. The risks and perils of the use of permanent catheters are well recognised. Although most realise that the infection risk for a patient with a catheter is twice that of a patient with an AV fistula, fewer people will know that the infectious risk for a PD patient is equal to that of an AV fistula, as most consider infection to be “the” problem of PD.

A second important advantage of PD first is the preservation of residual renal function (RRF). Diabetic patients tend to lose their RRF more rapidly than non-diabetics, whereas preservation of RRF might just be of greater importance for them. There is more and more evidence that the accumulation of advanced glycation end products plays an important role in the emergence of diabetic complications like micro-angiopathy and polyneuropathy. Levels of AGEs are directly related to RRF. There is also evidence that in diabetics, further deterioration of RRF can be delayed substantially by starting them on PD on a somewhat earlier level than a residual GFR of 15ml/min, probably because the PD removes uraemic waste products that are nephrotoxic by themselves. In this regard, it is expected that the now low GDP containing solutions might even perform better than the old solutions. Some studies seem to support this hypothesis, whereas others, though different in set up and with different brands of solutions, did not find a difference.

It also seems logical that the risk of sudden cardiac death should be lower in PD as compared to HD, because of the continuous nature of the treatment. Indeed, after the weekend, HD patients have accumulation of fluids and potassium, leading to arrhythmias and sudden death. Also the rapid changes in volume status during the HD session seem to predispose to arrhythmias. It is quite conceivable that diabetics are even more prone to this type of complication: diabetics gain more weight in between dialysis sessions, because of their (hyperglycaemia driven) higher fluid intake, and they tolerate ultrafiltration less well, because of autonomous polyneuropathy and stiffer blood vessels.

Other advantages of PD first are just comparable for diabetics and non diabetics: cost-effectiveness, better quality of life, better employment, lower risk of (viral) nosocomial infection.

**Extending technique success in diabetic PD patients**

Major reasons for technique failure still remain membrane failure and peritonitis/ infection. It is not clear whether the peritoneal membrane has different properties in diabetics, as some authors do find a faster transport status, whereas others do not. There is evidence that a good control of blood glycaemia nearly completely abolishes the negative impact of diabetes in experimental models. Comparably, it might be that in centres not using hypertonic bags, and stressing good glycaemic control, no differences in membrane characteristics are present, whereas in centres using hypertonic exchanges, there are. Clinical studies reveal that control of serum glycaemia in its turn will lead to hyperosmolarity, thirst and thus more fluid intake, which by itself forces the patient to use more hypertonic exchanges. This vicious circle can only be broken by correct control of serum glycaemia, salt restriction and avoidance of hypertonic bags.

There is animal and human evidence that the peritoneal membrane “wears off” during time on peritoneal dialysis, by two distinct processes: thickening of the membrane by fibrosis and neo-angiogenesis, leading to increased solute transport rates and ultrafiltration failure.

As the underlying processes driving these findings slowly emerge, it also is apparent that we can prevent these changes from happening to a large extend.

Second, exposure of the membrane to glucose leads by itself to upregulation of TGF beta and epithelial to mesenchymal transition: avoidance of glucose as much as possible is thus of importance. Again, care should be
taken to avoid the vicious circle of using hypertonic bags to control fluid overload. Salt restriction is again the cornerstone of the treatment. Salt intake increases hyperosmolarity, leading to thirst and volume intake. Besides these volume mediated effects, salt has also direct negative influences: there is an upregulation of pro-fibrotic growth factors in the heart, and in the kidney, leading to hypertrophy of the left ventricle and to enhanced glomerular sclerosis respectively.

Also for peritonitis, the literature is somewhat conflictive whether diabetics should have higher incidence rates than non-diabetics. Again, tight glycaemic control might play a role, as hyperglycaemia might create the ideal environment for micro-organisms. More important however to my opinion is the presence of polyneuropathy and diabetic rethnopathy, leading to touch contamination. A thorough training process, with special attention to adapt the exchange to the needs and skills of the individual patient, and a fail proof connectology are therefore crucial to avoid peritonitis in diabetic patients.

Patient empowerment and PD first

One of the big advantages of PD first (and also of other home therapies) is that there is an absolute need of patient education and involvement. There is rising evidence that these “educated patients” have better outcome as compared to patients who just have a more passive approach to their disease. Jones et al demonstrated that in patients who took part in a well structured pre-dialysis educational programme, the risk related to “diabetes” on outcome was abolished. This is not quite surprising, as other large trials like UKPDS have clearly shown that good control of blood pressure and glycaemia substantially improves outcome. In contrast to general belief, good control of blood pressure and glycaemia has more to do with life style changes, like salt restriction, physical exercise, weight control, than just with “prescription of medication”. In this context, the importance of an educational team, like a PD training team, can not be overestimated. There is also evidence that patients in such well structured programmes have a slower decline or residual renal function, probably again related to better blood pressure control.

Conclusion

The concept of integrated care is the ideal treatment paradigm for diabetic patients. It offers them the multidisciplinary approach of their disease they deserve.

PD first is a valuable option that should be recommended to the diabetic patient during his/her educational process, because of the preservation of vascular access, and of residual renal function, and the lower risk of sudden cardiac death.

Good glycaemic control, salt restriction and absolute avoidance of hypertonic exchanges should preserve the peritoneal membrane as long as possible. A safe and easy to use connectology and a tailored training programme taking into account eventual polyneuropatic and visual disturbances should be provided to avoid infection.

References