NEW-ONSET DIABETES IN PERITONEAL DIALYSIS PATIENTS – WHICH PREDICTORS REALLY MATTER?

Worldwide, it is estimated that over 200,000 individuals with end-stage renal disease are treated with maintenance peritoneal dialysis (PD) (1). Although the total number of patients per million population treated with PD has continuously increased over the past 2 decades, the first years of the 21st century saw a declining proportional use of PD in developed countries (1). However, at least in the United States, this downward trend in proportional use has recently reversed, and recent years have seen a surge in adoption of PD among patients with end-stage renal disease, in part due to changes in reimbursement (2). In parallel, most contemporary comparative effectiveness studies published from around the world over the past decade comparing mortality among patients undergoing maintenance hemodialysis with that for patients treated with PD have either found no significant association between dialysis modality use and mortality risk, or lower risk for death for patients undergoing PD (3–5). Patients treated with PD avoid exposure to tunneled central venous catheters, do not experience treatment-related myocardial stunning, and likely have better preservation of residual kidney function compared with patients undergoing maintenance hemodialysis (6,7).

Despite these putative advantages of PD relative to hemodialysis, PD-specific potential risk factors for adverse outcomes also exist. Most notably, PD entails either intermittent or continuous exposure of the peritoneal cavity to large volumes of dialysate containing 1 of 3 osmotically active agents: glucose, icodextrin, or amino acids. Because icodextrin or amino acid-containing solutions are designed to be used for only a single exchange during a 24-hour period, the vast majority of dialysate used for PD worldwide contains glucose. Use of PD thus results in significant obligatory systemic carbohydrate absorption which varies from 50 – 150 g of glucose daily depending on the specifics of the PD regimen, as well as on each patient's peritoneal membrane solute transfer rate. For patients with pre-existing diabetes mellitus, higher PD-solution glucose concentration has been associated in clinical trials with worsened glycemic control as measured by either glycosylated hemoglobin or serum fructosamine (8,9). Of note, participants in these clinical trials were followed for a maximum of 12 months, and over that duration of follow-up, improved glycemic control did not translate into improvements in cardiac function, fat-free mass, or health-related quality of life. Indeed, although observational studies have suggested an increased risk for morbidity and mortality in diabetic PD patients with poor glycemic control, no randomized trial published to date has shown a beneficial impact of improved glycemic control or reduced glucose exposure on clinically meaningful patient outcomes (10).

In contrast to such data regarding diabetic PD patients, very little is known about which patient- or treatment-related factors predict the development of new-onset diabetes mellitus or impaired glucose tolerance following initiation of PD in patients without pre-existing diabetes mellitus. There are several possible mechanisms which might explain the development of new-onset diabetes or elevated fasting glucose in patients with end-stage renal disease, and these include weight gain with amelioration of uremic anorexia and protein-energy wasting, changes in insulin resistance with loss of residual kidney function, and unmasking of previously undiagnosed diabetes. Inflammation is a clearly established risk factor for impaired glucose tolerance (11), and PD patients are known to have a high burden of both systemic and intra-peritoneal inflammation (12). Additionally, for patients undergoing PD, obligatory carbohydrate absorption with PD solutions has been considered to be an additional potential risk. However, 2 recent studies from Taiwan have compared the risk of new-onset diabetes mellitus among incident hemodialysis and PD patients and have found either an equivalent or lower risk among patients starting PD (13,14). Beyond this comparison with hemodialysis, however, there remains a substantial gap in understanding regarding risk factors and predictors of new-onset diabetes for patients initiating PD therapy.

It is within this context that Dong and colleagues report, in this issue of *Peritoneal Dialysis International*, their findings from a prospective cohort study investigating baseline and time-varying predictors of new-onset diabetes or impaired glucose tolerance in incident PD patients at a single center in China (15). Baseline information on demographics and co-existing illnesses was collected immediately prior to PD catheter placement. Laboratory measurements, blood pressure, dialysis regimen, and dietary parameters were recorded within the first 3 months after initiation of PD, and subsequent values were averaged for each 6-month period of follow-up. Laboratory measurements included markers of systemic inflammation, including C-reactive protein. Twenty-four-hour glucose absorption via dialysate was calculated for each patient at least every 3 months, with subsequent calculation of dialysate energy absorption. Patients also completed multi-day food diaries to allow calculation of time-varying dietary carbohydrate intake. Perhaps most importantly, the authors used a rigorous definition of a composite outcome of new-onset diabetes or impaired glucose tolerance endorsed by the American Diabetes Association, which included a true fasting plasma glucose or an oral glucose tolerance test (16). Fasting plasma glucose values were measured after a 10-hour period in which the

abdomen was drained of all dialysate, an important measure to ensure diagnostic accuracy given the continuous carbohydrate absorption in the presence of glucose-containing PD fluid. Of note, hemoglobin A1C was not used to define the primary endpoint, an additional important strength given that glycosylated hemoglobin has been shown in several studies to underestimate glycemic control in patients with end-stage renal disease (17).

Over a median follow-up of nearly 3 years, 5% of the participants in the study developed new-onset diabetes or impaired glucose tolerance (15). In a multivariate regression model, only baseline age, baseline and time-varying body mass index, and time-varying C-reactive protein were associated with occurrence of the primary composite outcome. Although not assessed in a multivariate model, baseline blood glucose and time-dependent increases in glucose concentrations were also associated with new-onset diabetes or impaired glucose tolerance.

The results of the study by Dong and colleagues, while not without limitations, provide an important contribution to the literature and at least partially bridge the gap in knowledge regarding predictors of new-onset diabetes and impaired glucose tolerance in incident PD patients. Perhaps what was most informative about the main findings of the study was not which factors were most predictive of diabetes onset, but rather which factors did not show significant predictive value. Specifically, neither dietary energy intake nor dialysate glucose absorption were predictive of the composite primary outcome, even in unadjusted analyses (15). Although dialysate glucose absorption is certainly affected by peritoneal membrane transport characteristics, the predominant factor influencing such absorption is the glycemic load provided by the glucose content of each patient's PD regimen. Thus, one interpretation of the findings of Dong and colleagues is that dialysate glucose content is not associated with subsequent development of diabetes mellitus, at least over the median follow-up period of approximately 3 years in this study. This finding supports those of other observational studies showing an inconsistent association between dialysate glucose content and outcomes in PD patients. In an early study of 97 continuous ambulatory PD patients, Davies and colleagues showed no difference in 2-year survival between PD patients with higher and those with lower dialysate glucose absorption (18). Similarly, Wu and colleagues found no association of average dialysate glucose concentration among 90 incident PD patients in the first 6 months after initiation of dialysis, although patients requiring higher glucose concentrations were more likely to transfer to hemodialysis (19). Although a second study from the same group did report an increased risk for death in patients prescribed higher glucose-containing PD solutions, this study used time-dependent exposure methods raising concerns regarding reverse causality (20). Indeed, all 3 of these observational studies were at risk of substantial residual confounding related to unmeasured factors (such as volume overload or residual kidney function) predictive of death that also cause

clinicians to prescribe PD regimens containing dialysate with higher glucose content. The study by Dong *et al.* is less likely to be confounded by unmeasured volume overload, both because the investigators accounted for time-varying body mass index, but also because volume overload is unlikely to confound the association between dialysate glucose content and incident diabetes. The results of this study thus add to the growing body of literature challenging the assertion that high glucose-containing PD solutions increase risk of adverse outcomes.

Beyond their null findings regarding dialysate and dietary glucose absorption, Dong and colleagues identified a longitudinal pattern of increasing plasma glucose in PD patients who go on to develop new-onset diabetes or impaired fasting glucose (15). In identifying this trend, the investigators highlight an important unanswered question, namely whether intervening in the care of such non-diabetic PD patients to control blood sugars either with insulin, oral hypoglycemic agents, or alterations to the PD regimen results in improvement in clinical outcomes. This question, however, necessarily should be followed by the caveat that even if such interventions affect the incidence of new diabetes diagnosis, no published study has shown that this would translate into true clinical benefit with respect to morbidity or mortality.

One important limitation of the analysis conducted by Dong and colleagues is that there was a high rate of mortality and other censoring reasons relative to the rate of development of new-onset diabetes or impaired glucose tolerance. Occurrence of the competing risks of death, transfer to hemodialysis, and transplant increases the possibility of a type II error and thus may mask the true prognostic value of key predictors such as the dialysate glucose absorption or dietary energy intake. Other predictors that showed a trend toward significance that may have been affected by type II error include dialysis adequacy, as assessed by Kt/V, and serum lipid profiles.

The finding that systemic inflammation as measured by serum C-reactive protein was associated with subsequent development of diabetes or impaired fasting glucose, even after adjustment for potential confounders, is an intriguing one. Chronic inflammation is known to induce insulin resistance, likely by induction of pro-inflammatory cytokines, and this pathophysiologic connection may be enhanced in patients with kidney disease. In non-dialysis patients with type 2 diabetes, blockade of the pro-inflammatory interleukin-1 receptor with the recombinant interleukin-1 receptor antagonist anakinra has been shown to reduce glycated hemoglobin levels as well as plasma markers of inflammation (21). To date, there are few published data reporting on the effect of anti-inflammatory therapy on either glycemic control or development of impaired fasting glucose among patients with end-stage renal disease. The currently recruiting Nutrition, Inflammation and Insulin Resistance in End-Stage Renal Disease (INSPIRED) trial (NCT02278562) will test the effect of anakinra on changes in insulin resistance as measured by glucose disposal rate. Additionally, the National Institutes of Health (NIH)-funded Hemodialysis Novel Therapies (HDNT)

Consortium is currently in the planning stage for a randomized clinical trial of the effect of anakinra on biomarkers of systemic inflammation and clinical outcomes in hemodialysis patients (22). If the results of the INSPIRED or HDNT trial suggest potential benefit, then future trials will need to be adequately powered to determine whether improvements in insulin resistance or systemic inflammation in patients with end-stage renal disease translate into real clinical benefit. Similarly, the findings of recent small studies showing a benefit of therapies as diverse as carnitine (23), thiazolidinediones (24), and angiotensin receptor blockers (25) on insulin resistance in PD patients need to be confirmed in larger multicenter randomized controlled trials and extended to assess whether such improvement results in reductions in risk for death or other patient-oriented clinical outcomes.

Regardless of whether interventions are identified that improve insulin sensitivity and reduce the incidence of diabetes in PD patients, it is important to recognize that a compelling body of literature supports that glucose lowering likely requires many years to yield substantial macrovascular and cardiovascular benefits. Thus, notwithstanding the results of the study by Dong and colleagues, discussion of impaired glucose tolerance in PD patients should not obscure attention and energy focused on improving other key intermediate outcomes in this patient population, such as volume status. Indeed, it should be pointed out that in the aforementioned clinical trials testing the effect of glucose-sparing dialysate regimens on patient outcomes, individuals treated with such regimens experienced a higher rate of certain adverse effects, particularly volume overload (8).

In summary, the study by Dong and colleagues represents an important contribution to the literature on diabetes in patients undergoing PD that confirms the primacy of age and body mass index in predicting incident impaired glucose tolerance and emphasizes the role of inflammation on insulin sensitivity. Additionally, the observed absence of an association between dialysate glucose absorption and incident diabetes is just as important a finding, and adds to a body of literature suggesting that lowering the glucose content of PD solutions may not translate into clinically meaningful outcomes. Further multicenter studies including adequately powered randomized trials are needed to clarify this question, as well as to identify new potential targets for intervention to improve patient-oriented clinical outcomes for patients undergoing PD.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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