

## The impact of peritoneal glucose load on blood pressure in peritoneal dialysis patients

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### Abstract:

**Background:** Hypertension is considered well-known independent risk factors for cardiovascular morbidity and mortality in peritoneal dialysis (PD) patients. Cardiovascular complications are the main cause of morbidity and mortality in patients with end-stage renal disease and dialysis patients. Peritoneal glucose load (PGL) contributes to the development of cumulative peritoneal membrane damage and increased permeability, leading to fluid accumulation and elevated blood pressure. The effects of PGL on hydration status, systemic inflammation, left ventricular mass, depression and male sexual dysfunction among PD patients was evaluated in our peritoneal unit in several prospective cross sectional studies conducted in the last five years (2014-2018). The relationship between PGL and blood pressure was not investigated before. Based on the data obtained from the mentioned studies and additional data that received from the usual maintenance follow up visits, we evaluated retrospectively the influence of PGL on blood pressure in patients on maintenance PD. **Methods:** Office blood pressure measurements were used. If white coat hypertension is suspected, a 24 hour blood pressure study was performed to assess the patient's overall blood pressure profile using Mobil-O-Graph device for 24-hour ambulatory blood pressure monitoring (Manufacture: Industrielle Entwicklung Medizintechnik GmbH, D-52222 Stolberg, Germany). The hydration status was assessed by a whole-body bio-impedance technique (BIS) using a Fresenius Medical Care Body Composition Monitor (BCM) device (Fresenius Medical Care, Bad Homburg, Germany). The PGL was assessed by PGL index (PGLI), which refers to the net glucose content (monohydrated or un-hydrated) (g) in the PD solutions administered in the daily PD prescription divided by the dry body weight (kg) assessed by BIS. **Results:** 159 medical records of stable PD patients were evaluated retrospectively. Significant positive correlations were found between PGLI and mean arterial pressure (MAP), extracellular water (ECW)/intracellular water (ICW) ratio and HbA1c. MAP, ECW/ICW ratio and HbA1c were significantly higher in patients with  $PGLI > 3$  g/kg/day compared with those with  $PGLI \leq 3$  g/kg/day. **Conclusions:** PGL may be associated with higher blood pressure, over-hydration and poor glycemic control in PD patients. PGLI could be applied in managing PD patients as a practical tool for the quantitative assessment of the PGL. PGLI values below 3 g/kg/day should be targeted.

### Introduction

Since the introduction of continuous ambulatory peritoneal dialysis (CAPD) in the 1970s, there has been a progressive increase in the number of end-stage renal disease (ESRD) patients undergoing peritoneal dialysis (PD) over the last 4 decades. Current data

suggest that 348,000 patients receive PD worldwide, representing approximately 9% of the global ESRD population. Early experience with PD revealed concerns about safety and efficacy of the modality, as well as higher mortality rates compared to in-center hemodialysis (HD). Over time, there have been substantial improvements in the clinical application of PD and since the mid-1990s there has been a significantly larger reduction in the risk of death in patients undergoing PD compared to those treated with HD. More recently, several studies indicate PD and HD to have similar short-term (1–2 years) or long-term (up to 5 years) survival. Despite improvements in dialysis survival over the years, adjusted survival for PD patients is still poor and suboptimal with 67% of patients surviving at 3 years after ESRD onset.

A number of studies have tried to identify PD-specific risk factors that increase the risk of death in this patient population. An area of investigation has been glucose (dextrose), which is utilized as the crystalloid osmotic agent in standard PD solutions. Clinical concerns associated with the use of glucose-based PD solution include systemic metabolic effects and local biocompatibility effects on the peritoneum that over time may lead to peritoneal fibrosis. Several studies have examined the use of alternative osmotic agents (sorbitol, mannitol, xylitol, icodextrin); however, none have been shown to have a superior safety and efficacy profile compared to glucose. This paper presents an overview of glucose absorption from PD solutions, its associated metabolic complications, as well as an exercise-based strategy that we hypothesize could combat the detrimental effects of glucose absorption.

Glucose is low-priced, efficient, and easily metabolized, which is why it is the main osmotic agent in PD solutions. However, a high average PDGC might, over the long term, heighten the risk of mortality. Researchers in Taiwan performed a retrospective analysis of 90 PD patients with varying average PDGC values, and they showed a borderline association between higher PDGC and worse patient survival (log-rank  $p = 0.10$ ) and a significantly worse technique survival (log-rank  $p = 0.002$ ). Their most recent study, which recruited 173 PD patients, indicated that higher average PDGC is significantly correlated with worse patient survival (log-rank  $p = 0.03$ ) and technique survival (log-rank  $p = 0.06$ ). Our study also showed that a higher PDGC was significantly associated with higher cumulative all-cause mortality in 716 CAPD patients. Moreover, we found that CAPD patients with a higher PDGC experienced a significant increase in cumulative CVD mortality, a finding that has not previously been reported.

Cardiovascular disease remains the leading cause of mortality in patients with ESRD, and cardiac and cerebrovascular causes account

for 65% of mortality in ESRD patients receiving long-term PD. In our study, CVD mortality was also the leading cause of all-cause death. In implementing specific treatment strategies, an assessment of CVD mortality predictors is important. Several modifiable risk factors associated with CVD mortality in ESRD patients have been found. In 25 588 patients on hemodialysis therapy, found that higher levels of calcium, phosphorus, and parathyroid hormone were correlated with increased CVD mortality. suggested that serum non-high-density lipoprotein cholesterol was a significant CVD mortality predictor in chronic hemodialysis patients. Hypoalbuminemia and higher C-reactive protein were found to be risk factors for CVD mortality in Japanese hemodialysis patients. However, showed that improvement of hyperphosphatemia, dyslipidemia, hypertension, and anemia did not result in an effective reduction in CVD mortality in ESRD patients.

Our study showed that high PDGC independently predicted all-cause mortality in CAPD patients. Moreover, high PDGC was also an independent risk factor for CVD mortality. Although reported that higher PDGC is associated with significantly worse patient survival (HR: 6.23; 95% CI: 1.26 to 30.74) in PD patients, the authors did not discuss the relationship between high PDGC and CVD mortality. Indeed, higher PDGC in PD solution is usually correlated with worse fluid control, more peritoneal damage, and more glucose uptake from the peritoneum. In addition, more glucose uptake from the peritoneum leads to an increase in insulin resistance and high blood glucose, resulting in DM in the long term. High average PDGC induces metabolic syndrome, with manifestations of hyperglycemia, hypertension, dyslipidemia, and overweight. Mortality from CVD is higher in PD patients with metabolic syndrome than in those without metabolic syndrome. Many studies have suggested that applying low-glucose regimens is a promising strategy to preserve peritoneal membrane integrity and RRF in PD patients. Although our study suggested that lower PDGC was associated with lower all-cause and CVD mortality in CAPD patients, large randomized trials are required to confirm the benefit of low-glucose regimens on clinical outcomes.

For better control of PDGC in PD patients, we investigated risk factors for high PDGC by ordinal logistic regression. We found that, compared with lower PDGC, higher PDGC was significantly correlated with older age, low RRF, and high D/P Cr. Older PD patients often have malnutrition and more comorbidities. Low RRF and a high peritoneal transport rate are associated with higher overall mortality in PD patients. reported that the rate of RRF decline is associated with all-cause mortality and technique survival in patients on long-term PD. A meta-analysis showed that a higher peritoneal transport rate is significantly associated with higher patient mortality. A higher peritoneal transport rate is also a risk factor for rapid loss of RRF, which may lead to dialysis inadequacy in PD patients. Lower RRF and a higher peritoneal transport rate are correlated with higher peritoneal glucose exposure. Patients with low RRF and a high peritoneal transport rate are prone to fluid overload, which requires high PDGC to eliminate overhydration. In our study, high PDGC was an independent risk factor for all-cause and CVD death after adjustment for RRF, Kt/V, and D/P Cr. Indeed, high PDGC may aggravate peritoneal membrane damage and induce ultrafiltration failure, which both contribute to increased mortality in the long term. Preserving RRF and strengthening management in high peritoneal transport may therefore help to break this vicious cycle and reduce all-cause and CVD mortality in CAPD patients.

#### **Conclusion:**

Our study shows that CAPD patients with higher PDGC experience higher all-cause and CVD mortality than do those with lower PDGC. High PDGC independently predicted all-cause and CVD mortality in long-term CAPD patients. Older age, low RRF, and high D/P Cr are independently associated with high PDGC in CAPD patients.