Impact of diabetes on extracellular volume status in patients initiating peritoneal dialysis

[1]Aniema Udo MD, Catriona Goodlad MD[2], Andrew Davenport FRCP[2]

[1]Dialysis Unit, University of Uyo Teaching Hospital, Akwa Ibom State, Nigeria
[2]UCL Centre for Nephrology, University College London, Royal Free Hospital, London, UK

Aniema Udo aniodiong@yahoo.com
Catriona Goodlad c.goodlad@nhs.net
Andrew Davenport andrewdavenport@nhs.uk

Address for correspondence
Andrew Davenport andrewdavenport@nhs.net

contact andrewdavenport@nhs.net
UCL Centre for Nephrology, Royal Free Hospital, University College London, Rowland Hill Street, London NW3 2PF
tel 44-2074726457 fax 44-2073178591

short title increased volume status in diabetic peritoneal dialysis patients

key words bioimpedance peritoneal dialysis muscle mass fat mass extracellular water intracellular water albumin

word count
abstract 245
body 2069
figures 1
tables 4
references 38
supplemental table 1
supplemental detailed methods

Funding Royal Free Hospital and Aniema Aniodong was in receipt of a scholarship from the European Renal Association – European Dialysis & Transplant Association

No author has any conflict of interest

Abstract

Background

Recent reports have highlighted that diabetic patients with kidney failure are at increased risk of technique failure and transfer to haemodialysis within 90 days of initiating peritoneal dialysis. We wished to determine whether there were differences between diabetic and non-diabetic patients within the first 3 months of starting peritoneal dialysis (PD).

Methods

We reviewed results of corresponding bioimpedance and the 1st test of peritoneal membrane function in consecutive patients, 6-10 weeks after initiating PD electively.

Results

386 adult patients, 230 males (59.6%), 152 (39.4%) diabetic, 188 (48.7%) white ethnicity, mean age 57.3 ±16.9 years were studied. Although weight, residual renal function and peritoneal clearances were not different, diabetic patients had greater extracellular water to total body water (ECW/TBW) (40.4±1.1 vs 39.2±1.4) and %ECW excess (9.6 (6.3-12.3) vs 4.9 (0.7-8.9)), lower serum albumin (35.2±4.7 vs 37.8±4.9 g/L), greater fat mass index (9.5±4.2 vs 7.7±4.2), and although mean arterial blood pressure was similar, arterial pulse pressure was greater 66.9±10.8 vs 54.3±17.3 mmHg, all p<0.001. On multivariate analysis, glycated haemoglobin was associated with pulse pressure (standardised β 0.24, p<0.001), N terminal brain natriuretic peptide (β 0.24, p<0.001), ECW/TBW (β

0.19, p=0.012), and negatively with serum albumin (β- 0.14, p=0.033) and creatinine (β- 0.18, p=0.02).

Conclusion

Diabetic patients electively starting PD were found to have greater ECW/TBW ratios and ECW excess 6-10 weeks after starting PD compared to non-diabetics, despite similar peritoneal membrane function. Increased ECW could predispose diabetic patients to be at greater risk of volume overload

Introduction

More than 300,000 patients with chronic kidney disease are now treated by peritoneal dialysis worldwide. Although some of this expansion in peritoneal dialysis has been due to a peritoneal dialysis first approach adopted by some countries in the Asia-Pacific region, there have been programmes to increase patient uptake in both North America and the UK. However, the average duration of treatment with peritoneal dialysis remains much less than that for haemodialysis, with peritonitis [1] and ultrafiltration failure being the commonest causes of technique failure for patients established on peritoneal dialysis [2]. Although peritoneal dialysis may incur lower health care treatment costs, episodes of peritonitis and acute transfer to haemodialysis considerably increase health care expenditure [3]. A recent study from North America reported that almost 30% of patients initiating peritoneal dialysis changed modality to haemodialysis within the first 90 days [4].

Diabetic patients have been reported to be are at greater risk of modality transfer to haemodialysis [5]. It is unclear as to whether this is due to glucose control or additional co-morbidities associated with diabetes and chronic kidney disease. Diabetic patients established on peritoneal dialysis have been reported to have accelerated loss of residual renal function and weight gain, which could be associated with extracellular water expansion and ultrafiltration failure [6,7].

However diabetic patients have also been reported to be at risk of early transfer to haemodialysis within the first 90 days of treatment [4]. As such we wished to review whether there were differences in peritoneal membrane function and volume assessments in diabetic patients attending for their first assessment of peritoneal membrane function 6-10 weeks after completing peritoneal dialysis training compared to non-diabetic patients.

Patients and methods

We reviewed the results of consecutive adult patients attending for their first assessment of peritoneal membrane function between 6 and 10 weeks after completing peritoneal dialysis training [8], who had corresponding bioimpedance assessments. Detailed methods are described in the supplemental methods section. Patients had started peritoneal dialysis electively, and none as an emergency, and no patient had suffered peritonitis since starting dialysis.

Patient related data was obtained from hospital computerised records and co-morbidity assessed using the Stoke-Davies grading scales [9].

This retrospective audit of standard routine clinical practice fulfilled the UK NHS guideline for clinical audit and service development (UK NHS guidelines for clinical audit and service development, available at http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf, and http://www.gov.uk/government/publications/health-research-ethics-committees-governancearrangements). All patient data was appropriately anonymised.

Statistical analysis

Statistical analysis was by t test, or Man Whitney U analysis, Anova or Kruskal Wallis with appropriate post-hoc correction for multiple analyses, and by Chi square test or Fisher's exact test. Spearman analysis was used for univariate analysis, and ancova for extracellular water measurements prior to and after starting PD, and then non-parametric data was log transformed for multivariable step backward linear analysis, using all variables with a $p<0.1$ correlation, with variables excluded if not statistically significant, unless they improved the model fit. Models were checked for variable inflation factor and collinearity (GraphPad Prism version 6.0, San Diego, USA, SPSS 24, University Chicago, USA). Data are presented as mean ± standard deviation, median (inter quartile range) or as a percentage. Statistical significance was taken at $p<0.05$.

Results

We reviewed the results of peritoneal membrane testing in 386 adult patients, 230 males (59.6%), 152 diabetic (39.4%), mean age 57.3 ±16.9 years, median timing of PET 8 weeks (6-10). Most patients were of white ethnicity, 188 (48.7%), followed by African-Afro-Caribbean 91 (23.6%), South Asian 80 (20.7%), and Far Asian 22 (5.7%). 78 (20.2%) patients were treated by continuous ambulatory peritoneal dialysis (CAPD), 87 (22.5%) by automated peritoneal dialysis cycler (APD) with no day time exchange, and 221 (57.3%) by APD with a day time exchange. 294 patients (76.8%) were treated with one 7.5% icodextrin exchange, 126 were prescribed one or more 22.7 g/L dextrose exchanges (32.9%), and no patient used greater glucose concentrations. Eighty one (21%) patients were prescribed neutral pH dialysates (Physioneal, Baxter Health Corporation, Deerfield, Illinois, USA). At 6 months, 331 (85.8%) patients remained on peritoneal dialysis, 24 (6.2%) had been transplanted, 26 (6.7%) transferred to haemodialysis (supplemental table) and 7 (1.8%) had died.

Diabetic patients were older, and there were more non-white diabetic patients from ($X2=15.1 p=0.005$) (table 1). Although body weight was similar, diabetic subjects had greater body mass index (BMI). Mean arterial blood pressure was similar between diabetics and non-diabetics, but diabetic patients were prescribed more anti-hypertensive medications ($X2=16.8$, $p=0.005$), and had a higher pulse pressure (table 1). Diabetic patients had lower serum cholesterol and triglyceride concentrations and more were prescribed HMG CoA3 reductase inhibitors (statins). C reactive protein concentration and serum albumin lower. 98 (41.9%) non-diabetic patients had grade one co-morbidity and

14 (6%) grade 2, compared to 72.4% of diabetics with grade one co-morbidity and 27.6% grade 2 ($X2=121.7$, $p<0.001$). At 6 months 84.3 % of diabetics remained on peritoneal dialysis and 10.5% had transferred to haemodialysis, compared to 86.7% and 4.3% for the non-diabetics.

As peritoneal clearances, may be affected by body size, we analysed peritoneal membrane function separately for male and female patients (table 2). As expected, male patients had greater weight with greater muscle mass and less body fat. There were no differences in residual renal clearances or peritoneal or total clearance. Female diabetic patients were faster transporters than non-diabetics, but transporter status was similar between male diabetics and non-diabetics. Diabetic patients had greater body fat and increased ECW/TBW and excess ECW (Figure 1). NT-proBNP was higher in male diabetic patients and albumin lower in diabetics, with male diabetics having a lower estimated nPNA. Diabetic patients had greater co-morbidity, but there were no differences between the sexes.

Glycated haemoglobin results (reported in mmol/mol as per guidelines International Federation of Clinical Chemists (IFCC)) were available for 347 (89.9%) patients, including all diabetic patients. On univariate analysis, glycated haemoglobin was associated with mean arterial pressure, pulse pressure, ECW excess, body fat and C reactive protein (CRP) and lower serum cholesterol, sodium, albumin, urea and creatinine, nPNA and sodium excretion. However, on restricting analysis to those with diabetes, statistical significance was lower or lost (pulse pressure $r= 0.19$, $p=0.02$, ECW/TBW ratio $r =0.05$, $p=0.58$). On multi-

variable analysis (table 3), after excluding variables for collinearity, then pulse pressure, NT-proBNP and the ratio of ECW/TBW remained associated with glycated haemoglobin Whereas IFCC glycated haemoglobin was negatively associated with serum albumin and creatinine (table 4).

Bioimpedance measurements were available in a subset of 145 patients at the time of training prior to commencing peritoneal dialysis, and on ancova testing, comparing starting and then at the time of peritoneal membrane testing ECW/TBW and ECW excess were significantly greater for diabetic patients ($f=12.7$, $f=13.1$, respectively, $p=0.001$). The ratio of ECW/TBW was similar starting peritoneal dialysis, but increased for the diabetic cohort (starting 39.2 ± 1.6 vs 39.1 ± 1.6 and at peritoneal membrane testing 39.4 ± 1.4 vs 39.1 ± 1.4).

Discussion

Previous reports have shown that whereas haemodialysis patients have a change in hydration status with dialysis sessions, peritoneal dialysis patients are generally volume expanded with an increased ECW/TBW ratio [10]. However, this ECW expansion does not necessarily reflect increased plasma volume, as ECW excess does not increase peritoneal ultrafiltration [7] or preserve residual renal function [11]. Some studies have suggested that this increase in ECW may be secondary to increased vascular permeability and albumin transfer into interstitial tissues [12]. As such ECW expansion, has been reported to be both associated with increased risk of peritoneal dialysis technique failure [2] and patient mortality [13].

Patients with faster peritoneal transport may be at risk of retaining sodium and fluid due to faster loss of the peritoneal osmotic glucose gradient. We found that female diabetic patients had faster PET transport for creatinine and total proteins, and greater glucose absorption but there were no differences between male patients. However, we found no differences in net sodium balance. Faster transporter status can also be secondary to greater intra-peritoneal capillary surface area, which increases with body size, and can also be affected by hyperglycaemia causing vasodilatation [14]. However, the effects of faster transport status can be reduced using icodextrin [15] and the use of APD cyclers with shorter dwell times. As such more recent studies have not shown an association between faster transporter status in diabetic peritoneal dialysis patients and survival [16]. Although other studies have reported an association between faster peritoneal protein transport, which also may be increased by local or systemic inflammation [17], and hyperglycaemia may induce inflammatory vascular changes [14]. Although systolic blood pressure, and mean arterial blood pressure were similar between diabetic and non-diabetic patients, our diabetic subjects were prescribed more anti-hypertensive agents and we did note that diabetic patients had increased arterial pulse pressure, suggesting stiffening of major arteries. Pulse wave velocity has been reported to be greater in PD patients with increased ECW expansion [18]. However, this was a relatively small study and underpowered to determine whether there were differences for diabetic patients. Diabetic patients are recognised to be at risk

of arterial calcification, and more recently sodium deposition in the vasculature [19,20,].

We found that diabetic patients had lower serum cholesterol and triglyceride concentrations. This may have been due to the greater prescription of statins in the diabetic patients, and although diabetic patients used more 22.7 g/L glucose dialysates they also had a high usage of icodextrin dialysates, with 26.5% also using nutrineal. The combination of icodextrin and nutrineal has been shown to lower both cholesterol and triglycerides in diabetic peritoneal dialysis patients [21]. In addition to lower serum cholesterol, diabetic patients had lower serum sodium, urea, creatinine and albumin concentrations. Previous reports in peritoneal dialysis patients have suggested that fluid retention could lead to a dilutional effect [22]. However, hyperglycaemia can interfere with the standard laboratory measurement of sodium [23], and once we corrected for the glucose effect, serum sodium concentrations were not different, suggesting that these differences were not simply due to dilution. The lower urea and creatinine concentrations taken along with the lower nPNA could result from suggest lower dietary protein intake and creatinine generation. Some studies have suggested that diabetic patients and those with greater co-morbidity have lower active energy expenditure [24]. Bioimpedance can be used to assess body composition [25], and we noted that diabetic patients had more body fat, and male diabetic patients had less muscle mass when adjusted to height. Our diabetic patients were older, and body composition can change with age. To minimise age related changes, we determined ECW excess, by comparing

measured ECW with that predicted from ICW normative data Diabetic patients had greater ECW than predicted, and in the subgroup who had starting bioimpedance data, this increased significantly in the diabetic patients since starting PD.

On univariate analysis, glycated haemoglobin was negatively associated with total sodium losses, such that patients with higher IFCC glycated haemoglobin had lower sodium losses, suggesting that they could be at risk of sodium retention. This would be in keeping with the associations between increasing glycated haemoglobin and increased ECW/TBW and NTproBNP, along with arterial pulse pressure. However, increasing co-morbidity and inflammation have also been observed to increase ECW/TBW and NTproBNP [15]. This interaction would support the association with lower serum albumin, creatinine and nPNA. However, when analyses were restricted to the diabetic patients alone, then there was no association between ECW excess and glycated haemoglobin, suggesting the association is for diabetics, rather than glucose control per se. There is controversy as to the effect of diabetic control on outcomes in peritoneal dialysis patients [26,27]. The different results reported by studies may be related to confounders including whether single time point measurements of glycated haemoglobin reflect long-term time averaged diabetic control, the duration of diabetes and also insulin resistance, so called "pre-diabetes", and additional factors which may specifically affect glycated haemoglobin concentrations in PD patients [28].

Although many diabetic patients with chronic kidney disease are successfully treated by peritoneal dialysis [29], other reports have suggested that diabetic patients are more likely to suffer early technique failure and transfer to haemodialysis [4]. Comparing diabetic patients at their first assessment of peritoneal membrane function we found that diabetic patients had evidence of ECW excess compared to non-diabetics as the measured ECW was greater than the ECW expected for the ICW, suggesting that diabetic patients had greater ECW. This association between ECW expansion and diabetes may potentially increase the risk of technique failure, but this hypothesis would require formal testing in a prospective trial.

Funding Royal Free Hospital and Aniema Udo was in receipt of a scholarship from the European Renal Association – European Dialysis & Transplant Association
No author has any conflict of interest

References

1. Davenport A. Peritonitis remains the major clinical complication of peritoneal dialysis: the London, UK, peritonitis audit 2002-2003. Perit Dial Int. 2009;29(3):297-302
2. Fan S, Davenport A. The importance of overhydration in determining peritoneal dialysis technique failure and patient survival in anuric patients. Int J Artif Organs. 2015 Nov;38(11):575-9
3. Li B, Cairns JA, Fotheringham J, Tomson CR, Forsythe JL, Watson C, Metcalfe W, Fogarty DG, Draper H, Oniscu GC, Dudley C, Johnson RJ, Roderick P, Leydon G, Bradley JA, Ravanan R. Understanding cost of care for patients on renal replacement therapy: looking beyond fixed tariffs. Nephrol Dial Transplant. 2015;30(10):1726-34
4. Pulliam J, Li NC, Maddux F, Hakim R, Finkelstein FO, Lacson E Jr. First-year outcomes of incident peritoneal dialysis patients in the United States. Am J Kidney Dis. 2014;64(5):761-9
5. Ozener C, Arikan H, Karayaylali I, Utas C, Bozfakioglu S, Akpolat T, Ataman R, Ersoy F, Camsari T, Yavuz M, Akcicek F, Yilmaz ME. The impact of diabetes mellitus on peritoneal dialysis: the Turkey Multicenter Clinic Study. Ren Fail. 2014;36(2):149-53
6. Kim JK, Kim YS, Song YR, Kim HJ, Kim SG, Moon SJ. Excessive Weight Gain during the First Year of Peritoneal Dialysis Is Associated with Inflammation, Diabetes Mellitus, and a Rapid Decrease in Residual Renal Function. PLoS One. 2015 Sep 25;10(9):e0139033. doi: 10.1371/journal.pone.0139033. eCollection 2015 PMID: 26406589
7. Davenport A, Willicombe MK. Does diabetes mellitus predispose to increased fluid overload in peritoneal dialysis patients? Nephron Clin Pract. 2010;114(1):c60-6

8. NKF-K/DOQI Clinical practice guidelines for peritoneal dialysis adequacy: Clinical practice recommendations for peritoneal dialysis adequacy Am J Kid Dis 2006; 48 [Suppl 1]: S98–S158

9. Davies SJ. Assessment of comorbidity in peritoneal dialysis patients. Contrib Nephrol. 2003; 140: 98-103

10. Papakrivopoulou E, Booth J, Pinney J, Davenport A. Comparison of volume status in asymptomatic haemodialysis and peritoneal dialysis outpatients. Nephron Extra. 2012;2(1):48-54

11. McCafferty K, Fan S, Davenport A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. Kidney Int. 2014 Jan;85(1):151-7.

12. John B, Tan BK, Dainty S, Spanel P, Smith D, Davies SJ. Plasma volume, albumin, and fluid status in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2010;5(8):1463-70.

13. O'Lone EL, Visser A, Finney H, Fan SL. Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival. Nephrol Dial Transplant. 2014;29(7):1430-7

14. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Proinflammatory effects of glucose and anti-inflammatory effect of insulin: relevance to cardiovascular disease. Am J Cardiol. 2007;99(4A):15B-26B

15. Davies SJ, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, Bosselmann HP, Heimbürger O, Simonsen O, Davenport A, Tranaeus A, Divino Filho JC. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. J Am Soc Nephrol. 2003 14(9):2338-44

16. Huang N, Chen J, Fan L, Zhou Q, Xu Q, Xu R, Xiong L, Yu X, Mao H. High peritoneal transport status was not associated with mortality in peritoneal dialysis patients with diabetes. PLoS One. 2014 Oct 16;9(10):e110445. doi: 10.1371/journal.pone.0110445. eCollection 2014. PMID: 25329459

17. Chang TI, Kang EW, Lee YK, Shin SK. Higher peritoneal protein clearance as a risk factor for cardiovascular disease in peritoneal dialysis patient. PLoS One. 2013;8(2):e56223. doi: 10.1371 PMID: 23418538

18. Kocyigit I, Sipahioglu MH, Orscelik O, Unal A, Celik A, Abbas SR, Zhu F, Tokgoz B, Dogan A, Oymak O, Kotanko P, Levin NW. The association between arterial stiffness and fluid status in peritoneal dialysis patients. Perit Dial Int. 2014;34(7):781-

19. Lambert J, Pijpers R, van Ittersum FJ, Comans EF, Aarsen M, Pieper EJ, Donker AJ, Stehouwer CD. Sodium, blood pressure, and arterial distensibility in insulin-dependent diabetes mellitus. Hypertension. 1997;30(5):1162-8

20. Kusche-Vihrog K, Schmitz B, Brand E. Salt controls endothelial and vascular phenotype. Pflugers Arch. 2015;467(3):499-512

21. Li PK, Culleton BF, Ariza A, Do JY, Johnson DW, Sanabria M, Shockley TR, Story K, Vatazin A, Verrelli M, Yu AW, Bargman JM; IMPENDIA and EDEN Study Groups. Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. J Am Soc Nephrol. 2013;24(11):1889-900

22. Jones CH, Wells L, Stoves J, Farquhar F, Woodrow G. Can a reduction in extracellular fluid volume result in increased serum albumin in peritoneal dialysis patients? Am J Kidney Dis. 2002;39(4):872-5.

23. Courivaud C, Davenport A. Measurement and interpretation of serum sodium in end-stage kidney disease patients. Semin Dial. 2014;27(6):542-4

24. 31. El-Kateb S, Sridharan S, Farrington K, Davenport A. Comparison of resting and total energy expenditure in peritoneal dialysis patients and body composition measured by dual-energy X-ray absorptiometry. Eur J Clin Nutr. 2016; 70(11):1337-1339

25. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int.2014; 86 (3):489-96

26. Park JI, Bae E, Kim YL, Kang SW, Yang CW, Kim NH, Lee JP, Kim DK, Joo KW, Kim YS, Lee H. Glycemic Control and Mortality in Diabetic Patients Undergoing Dialysis Focusing on the Effects of Age and Dialysis Type: A Prospective Cohort Study in Korea. PLoS One. 2015 Aug 18;10(8):e0136085. doi: 10.1371 PMID: 26285034

27. Adler A, Casula A, Steenkamp R, Fogarty D, Wilkie M, Tomlinson L, Nitsch D, Roderick P, Tomson CR. Association between glycemia and mortality in diabetic individuals on renal replacement therapy in the U.K. Diabetes Care. 2014;37(5):1304-11.

28. Coelho S, Rodrigues A. Hemoglobin A1c in patients on peritoneal dialysis: how should we interpret it? Ther Apher Dial. 2014;18(5):375-82

29. Fan S, Davenport A. Does increased glucose exposure lead to increased body fat and reduced lean body mass in anuric peritoneal dialysis patients? Eur J Clin Nutr. 2014;68(11):1253-4

Figure 1. Extracellular water excess compared to that expected for intracellular water for male and female patients [14]. *p<0.05 vs non-diabetics.

Table 1. Combined urinary urea and creatinine clearance (residual renal function). Results expressed as integer, mean ±SD, or median (interquartile range) or percentage.* p<0.05, ** <0.01, *** <0.001 vs non-diabetic

Table 2. Body composition determined by bioimpedance and residual renal and peritoneal clearances, and peritoneal membrane function (PET) for diabetic and

non-diabetic patients. Mean arterial pressure (MAP), fat and soft mass indexed to height (FMI and SMI). Intracellular water (ICW), extracellular water (ECW), 4 hour dialysate and serum samples (D4, S)) and time zero dialysate (D_0), ultrafiltration volume (UF). Combined urinary urea and creatinine clearance (residual renal function), and urea clearance ($Kt_{urea)}$, litres of creatinine (Lcreat), sodium (Na), normalised protein nitrogen appearance rate (nPNA), C reactive protein (CRP), N terminal brain natriuretic peptide (NTproBNP). International Federation Clinical Chemists (IFCC) measurement of glycated haemoglobin (IFCC). Stoke Davies co-morbidity grade (co-morbidity). Results expressed as integer, mean ±SD, or median (interquartile range) or percentage.* p<0.05, ** <0.01, *** <0.001 vs non-diabetic

Table 3: Spearman univariate associations with International Federation Clinical Chemists (IFCC) measurement of glycated haemoglobin (IFCC). Serum sodium not corrected for glucose.

Table 4; Step backward multivariable analysis using International Federation Clinical Chemists (IFCC) measurement of glycated haemoglobin (IFCC) which was log transformed. Unstandardised β (β) and standard error (StE) and standardised β (stβ), 95% confidence limits (95% CL). NT pro-brain natriuretic protein (NTproBNP), serum creatinine (creatinine), extracellular to total body water ratio (ECW/TBW). Model r=0.49, r^2 =0.25, adjusted r^2 = 0.23