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Serum Leptin in Peritoneal Dialysis: Is It a Useful Biomarker Following Peritonitis?

David W. Johnson [1*]

[1] Department of Nephrology, University of Queensland, Princess Alexandra Hospital, Brisbane, Australia

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Acute peritoneal dialysis (PD)-associated peritonitis stimulates peritoneal adipocytes to release large amounts of the adiocytokine, leptin, into the dialysate and serum. Based on recent research, the ensuing acute hyperleptinaemia is transient and may form an important link between chronic inflammation and malnutrition following peritonitis leading to important long-term sequelae for PD patients. Future longitudinal clinical studies evaluating the impact of acute peritonitis-induced hyperleptinemia on subsequent development of patient-level outcomes, such as malnutrition, inflammation, cardiovascular events, and technique and overall survival, are warranted.

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Over the past 30 years, peritoneal dialysis (PD) has become an established form of renal replacement therapy that is currently used to treat over 200,000 patients with end-stage renal disease worldwide (1). Patient survival on PD is at least comparable, and possibly superior, to that of patients receiving hemodialysis (HD) (2). However, the rate of technique failure, including both surgical technical and membrane failure, associated with PD is higher than that associated with HD (3). The identification of a biomarker that can reliably identify PD patients at high risk of technique failure at an early stage would be highly valuable.

One of the major factors underpinning the high technique failure rate of PD is structural and functional derangement of the peritoneal membrane and systemic inflammation following chronic exposure to conventional, "unphysiological" PD fluids that are characterized by acidic pH (5.0–5.8), high lactate concentrations (30–40 mmol/L), high osmolality (320–520 mOsm/kg), high glucose concentrations (31–236 mmol/L), and contamination by glucose degradation products (GDP) generated during the heat sterilization process (4). The bio-incompatible nature of these fluids results in both a negative impact on host defence, leading to a heightened risk of peritonitis, and a profibrotic effect on the peritoneal membrane, leading to ultrafiltration failure and/or impaired small solute clearance (5-7). A large body of basic science research in animal models and peritoneal cell culture systems has focused on the detrimental effects of conventional PD fluids on human peritoneal mesothelial cells, macrophages, and fibroblasts (7-9). However, recent research has highlighted that peritoneal adipocytes also exert important metabolic, pro-inflammatory, and atherogenic effects in PD patients via the secretion of a vast array of adipocytokines (10).

* *Corresponding author:* David W. Johnson, Department of Nephrology, ARTS Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, 4102 Brisbane Qld, Australia. Tel: +61-732405080, Fax: +61-732405480, *E-mail:* david_johnson@health.qld.gov.au

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One of the key adipocytokines released by peritoneal adipocytes is leptin, a 16-kDa protein product of the obesity (ob) gene, which plays key roles in appetite suppression (via stimulation of α-melanocyte stimulating hormone and antagonism of neuropeptide Y and anandamide), inflammation, and bone metabolism (11). Studies in an experimental mouse model of chronic kidney disease (CKD) have further suggested that leptin signalling through the hypothalamic melanocortin receptor 4 contributes to uremic cachexia. Because leptin is freely filtered at the glomerulus and degraded in the renal tubules, serum levels of leptin are significantly higher in CKD, HD, and PD patients than in individuals with normal renal function (12, 13). Exposure to glucose-containing PD fluid increases leptin secretion by murine adipocytes in vitro. A longitudinal, observational cohort study of 20 incident PD patients has demonstrated that serum leptin levels increased markedly to 189% of baseline levels at 1 month and to 260% at 3 months after commencing PD (14). The significant increase in leptin concentrations in PD patients may also be related to chronic hyperinsulinemia in response to high dialysate glucose content (15). Moreover, inflammation may lead to further increases in leptin secretion because ob gene expression has been shown to be significantly higher in PD patients with elevated C-reactive protein (CRP) levels (>25 mg/L) than in those without elevated levels (16). During acute peritonitis, leptin concentrations in the peritoneal dialysate effluent of patients increase more than threefold of that of PD controls, without signs and symptoms of inflammation, and continue to remain elevated at the time of hospital discharge (17). Receiver operating characteristic analyses revealed that peritoneal dialysate leptin concentrations greater than 11.0 ng/L had 58.3% sensitivity and 95.5% specificity for the diagnosis of acute peritonitis. Another prospective, observational cohort study of 42 PD patients with peritonitis showed that serum leptin levels increased significantly from baseline to days 1 and 7 in concert with serum CRP levels; however, the serum leptin levels returned to baseline by day 42 (18). The authors hypothesized that hyperleptinemia may act as an independent contributory factor linking chronic inflammation and malnutrition following peritonitis. Thus, leptin may represent a useful biomarker in PD patients, particularly following peritonitis episodes.

In the January issue of Nephro-Urology Monthly, Momeni and Seirafian (19) conducted a single-center, cross-sectional, observational cohort study of 75 prevalent PD patients to evaluate the relationship between serum leptin concentrations and history of peritonitis in the preceding year by using univariate general linear model statistical analysis. The principal finding of their study was a statistically significant, albeit weak, association between serum leptin concentration and the number of peritonitis episodes in the past 12 months. In keeping with the results of other studies (12, 20), Momeni and Seirafian (19) observed a statistically significant correlation of leptin levels with body mass index, but not with Kt/V or number of daily peritoneal exchanges. The authors concluded that serum leptin level was not a clinically useful indicator of prior peritonitis episodes; however, further investigations for examining the interaction between peritonitis and serum and dialysate leptin levels were warranted.

Although the study has been carefully conducted and makes valuable contribution to the knowledge in this area, it has limitations such as small sample size, retrospective evaluation of peritonitis history, use of prevalent PD patients (leading to possible Neyman bias), potential survivor bias (as patients experiencing peritonitis had to survive and remain on PD to be included in this study), and lack of multivariate adjustment for covariates that may have confounded the relationship between serum leptin levels and peritonitis history (i.e., body mass index). Moreover, serum leptin levels were determined by convenience sampling at variable and unspecified periods following peritonitis episodes, which may have limited the evaluation, and therefore the conclusions that could have been drawn.

How then should we incorporate the findings of Momeni and Seirafian into clinical practice? In my view, their findings provide several key messages. Firstly, there is increasing evidence that peritoneal adipose tissue does not simply assume a passive role in the storage of energy as fat, but instead, it is actively involved in the structural and functional peritoneal membrane alterations and systemic metabolic and inflammatory sequelae of PD through the release of metabolically active and pro-inflammatory cytokines, such as leptin. Secondly, acute peritonitis stimulates the release of substantial amounts of leptin from peritoneal adipocytes into the dialyzate and serum, and this release may form an important link between chronic inflammation and malnutrition following peritonitis. However, as Momeni and Seirafian have clearly shown in their investigation, this acute hyperleptinemia does not persist, and therefore, serum leptin levels are not suggestive of a patient's peritonitis history. Thus, whilst leptin meets the first 2 criteria of a good biomarker (presence in peripheral body tissue and/or fluid and easy detection by an assay that is both affordable and robust), it falls short of the third criterion (appearance associated as specifically as possible with damage of a particular tissue, preferably in a quantifiable manner). Nevertheless, acute PD-associated peritonitis results in appreciable, albeit transient, elevations in leptin levels, which may have important long-term consequences for PD patients. Future longitudinal clinical studies evaluating the impact of acute peritonitis-induced hyperleptinemia on subsequent development of patient-level outcomes, such as malnutrition, inflammation, cardiovascular events, and technique and overall survival, are warranted.

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References

1. Lameire N, Van Biesen W. Epidemiology of peritoneal dialysis: a story of believers and nonbelievers. *Nat Rev Nephrol*. 2010;**6**(2):75-82.
2. Vonesh EF, Snyder JJ, Foley RN, Collins AJ. Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? *Kidney Int Suppl*. 2006.**103**:S3-11.
3. Davies SJ, Phillips L, Naish PF, Russell GI. Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J Am Soc Nephrol*. 2001;**12**(5):1046-51.
4. Topley N. In vitro biocompatibility of bicarbonate-based peritoneal dialysis solutions. *Perit Dial Int*. 1997;**17**(1):42-7.
5. Topley N. Membrane longevity in peritoneal dialysis: impact of infection and bio-incompatible solutions. *Adv Ren Replace Ther*. 1998;**5**(3):179-84.
6. Pecoits-Filho R, Stenvinkel P, Heimburger O, Lindholm B. Beyond the membrane-the role of new PD solutions in enhancing global biocompatibility. *Kidney Int Suppl*. 2003. **88**:S124-32.
7. Witowski J, Jorres A. Effects of peritoneal dialysis solutions on the peritoneal membrane: clinical consequences. *Perit Dial Int*. 2005;**25** (Suppl 3):S31-4.
8. Schambye HT. Effect of different buffers on the biocompatibility of CAPD solutions. *Perit Dial Int*. 1996;**16** (Suppl 1):S130-6.
9. Nau B, Schmitt CP, Almeida M, Arbeiter K, Ardissino G, Bonzel KE, *et al.* BIOKID: randomized controlled trial comparing bicarbonate and lactate buffer in biocompatible peritoneal dialysis solutions in children [ISRCTN81137991]. *BMC Nephrol*. 2004;**5**:14.
10. Lai KN, Leung JC. Peritoneal adipocytes and their role in inflammation during peritoneal dialysis. *Mediators Inflamm*. 2010;**2010**:495416.
11. Bertherat J, Groussin L, Bertagna X. Mechanisms of disease: adrenocortical tumors–molecular advances and clinical perspectives. *Nat Clin Pract Endocrinol Metab*. 2006;**2**(11):632-41.
12. Parry RG, Johnson DW, Carey DG, Hibbins M, Chang W, Purdie D, *et al.* Serum leptin correlates with fat mass but not dietary energy intake in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int*. 1998;**18**(6):569-75.
13. Briley LP, Szczech LA. Leptin and renal disease. *Semin Dial*. 2006;**19**(1):54-9.
14. Kim DJ, Oh DJ, Kim B, Lim YH, Kang WH, Lee BH, *et al.* The effect of continuous ambulatory peritoneal dialysis on change in serum leptin. *Perit Dial Int*. 1999;**19** (Suppl 2):S172-5.
15. Kolaczynski JW, Nyce MR, Considine RV, Boden G, Nolan JJ, Henry R, *et al.* Acute and chronic effects of insulin on leptin production in humans: Studies in vivo and in vitro. *Diabetes*. 1996;**45**(5):699-701.
16. Nordfors L, Lonnqvist F, Heimburger O, Danielsson A, Schalling M, Stenvinkel P. Low leptin gene expression and hyperleptinemia in chronic renal failure. *Kidney Int*. 1998;**54**(4):1267-75.
17. Kolonko A, Chudek J, Wiecek A. Concentration of adipokines in peritoneal effluent: a new marker of acute peritonitis in peritoneal dialysis patients? *Perit Dial Int*. 2008;**28**(5):527-32.
18. Lam MF, Leung JC, Lo WK, Tam S, Chong MC, Lui SL, *et al.* Hyperleptinaemia and chronic inflammation after peritonitis predicts poor nutritional status and mortality in patients on peritoneal dialysis. *Nephrol Dial Transplant*. 2007;**22**(5):1445-50.
19. Momeni A, Seirafian s. Relationship between serum leptin level and peritonitis in CAPD patients. *Nephro-Urol Mon*. 2011;**3**(4): 272-5.
20. Kagan A, Haran N, Leschinsky L, Shuali N, Rapoport J. Leptin in CAPD patients: serum concentrations and peritoneal loss. *Nephrol Dial Transplant*. 1999;**14**(2):400-5.