

OBJECTIVE: It is known that glucose concentrations of peritoneal dialysis solutions are detrimental to the peritoneal membrane. In order to determine the effect of glucose concentration on cytokine levels of peritoneal fluid of continuous ambulatory peritoneal dialysis (CAPD) patients, a cross-sectional study was performed.

Methods: Nine non-diabetic CAPD patients participated in two 8-h dwell sessions of overnight exchanges in consecutive days, with 1.36% and 3.86% glucose containing peritoneal dialysis solutions (Baxter–Eczacıbaşı). Peritoneal dialysis fluid tumor necrosis factor (TNF)- α and interleukin (IL)-6 levels were measured.

Results: TNF- α levels after 1.36% and 3.86% glucose used dwells were 23 ± 14 pg/ml and 28 ± 4 pg/ml, respectively ($p = 0.78$). The IL-6 levels were 106 ± 57 pg/ml and 115 ± 63 pg/ml ($p = 0.81$), respectively.

Conclusion: In our *in vivo* study we found that the glucose concentration of the conventional lactate-based CAPD solution has no effect on basal IL-6 and TNF- α levels of peritoneal fluid. Further *in vivo* studies with non-lactate-based CAPD solutions are needed in order to determine the effect of glucose concentration *per se* on cytokine release.

Key words: Cytokines, Peritoneal dialysis, Peritoneal dialysis fluid, Glucose concentration

Effect of glucose concentration on peritoneal inflammatory cytokines in continuous ambulatory peritoneal dialysis patients

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Introduction

Peritoneal dialysis (PD) is established as a viable and successful alternative to hemodialysis for end-stage renal disease patients. However, impairment of peritoneal membrane function remains a major factor causing modality change in a significant number of patients on PD. *In vivo* studies in long-term PD have demonstrated diabetiform alterations of the peritoneum.¹ These alterations are accompanied by functional abnormalities, such as ultrafiltration failure or reduced solute clearance. In addition to the induction of pro-inflammatory and/or pro-fibrotic cytokines, animal and *in vitro* studies have highlighted the adverse effects of glucose-based peritoneal dialysis fluid (PDF) on resident peritoneal cells.^{2,3} Cytokines known to cause inflammatory reactions are called pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, IL-8, IL-12, IL-18, granulocyte-macrophage colony-stimulating factor and interferon- γ .⁴ Chemical insult to peritoneal mesothelial cells can induce the synthesis of cytokines, chemokines and growth factors, and is associated with accumulation and deposition of matrix proteins.⁵

In order to determine the effect of glucose concentration on cytokine levels of peritoneal fluid

of continuous ambulatory peritoneal dialysis (CAPD) patients, a cross-sectional study was performed.

Patients and methods

After informed consent was obtained, nine non-diabetic CAPD patients participated in two 8-h dwell sessions of overnight exchanges on consecutive days, with 1.36% and 3.86% glucose-containing PD solutions (Baxter–Eczacıbaşı). The patients (three females/six males; mean age, 44.9 ± 17.5 years) were stable on CAPD and had been free of peritonitis and any inflammatory conditions for more than 8 weeks. Dialysate samples were taken immediately after the dwell. PDF TNF- α and IL-6 levels were measured by using the commercial IMMULITE kits, which are a solid-phase, two-site chemiluminescent immunometric assay (Immullite, DPC, Los Angeles, CA, USA). The Wilcoxon *t*-test was used to compare cytokine levels.

Results

TNF- α levels after 1.36% and 3.86% glucose used dwells were 23 ± 14 pg/ml and 28 ± 4 pg/ml, respec-

tively ($p = 0.78$). IL-6 levels were 106 ± 57 pg/ml and 115 ± 63 pg/ml ($p = 0.81$), respectively (Fig. 1, Fig. 2).

Discussion

Earlier *in vitro* studies underlined the cytotoxic and inhibitory effects of conventional fluids on fundamental cell functions of macrophages and polymorphonuclear granulocytes, including their phagocytic capacity and their ability to secrete inflammatory cytokines.^{6,7} It was known that in CAPD patients without peritonitis spent dialysate IL-6 concentrations are several times higher than the serum levels, indicating local production of this cytokine in the peritoneal cavity.⁸ TNF- α levels of spent dialysate are lower than the serum levels, but in response to peritoneal inflammation these levels increase rapidly. Also, dialysate TNF- α levels may be affected by the dialysate configuration. Plum *et al.* reported that application of amino acid/bicarbonate-containing PDF resulted in significantly higher dialysate TNF concentrations when compared with glucose/bicarbonate-containing solutions.⁹ A limited number of *in vivo* studies analyzed the effects of different glucose concentrations on IL-6 and TNF- α release from peritoneal or peripheral blood macrophages, monocytes or mesothelial cells. Douvdevani *et al.* studied the *in vitro* effect of dialysis fluid on the basal and lipopolysaccharide stimulated release of IL-1 β and TNF- α by peritoneal macrophages and peripheral blood mononuclear cells (PBMC), and the time course and factors involved in this effect. They found that the presence or absence of glucose had no effect on cytokine production but pH and lactate are the important inhibitory factors.¹⁰

In another *in vitro* study Jorres *et al.* reported that, while bicarbonate and 1.5% glucose-based PD solution did not inhibit cytokine release (mononuclear leukocyte IL-6 and TNF- α release in response to bacterial lipopolysaccharide), bicarbonate and 4.25% glucose-based PD solution exerted > 80% inhibition.¹¹ Cendoroglo *et al.* investigated the effects of high glucose concentration, osmolarity, and heat

sterilization of PDFs on TNF- α production by PBMC and polymorphonuclear cell (PMN) functions. They found that high glucose concentration induced an increase in TNF- α production by unstimulated PBMCs, a decrease in TNF- α production by endotoxin-stimulated PBMCs, and an inhibition of PMN functions. These effects were also compared for different glucose concentrations when osmolarity was equally adjusted with mannitol and for different osmolarity levels when glucose was equally adjusted. They suggested that high glucose concentration, high osmolarity, and heat sterilization of PDF adversely affect PBMC and PMN functions.¹²

Cooker *et al.* reported that in CAPD patients treatment with bicarbonate/lactate is associated with decreased peritoneal IL-6 synthesis and decreased vascular endothelial growth factor secretion when compared with conventional glucose-based PDF.¹³ Serre *et al.* reported that in non-uremic individuals peritoneal lavage with dialysis fluid inhibited the cytokine production (IL-1, IL-6, IL-8, TNF- α and IL-1 β), and with isotonic NaCl cells produced less cytokines when compared with dialysis patients.¹⁴ When compared with conventional glucose-based PDF, human peritoneal mesothelial cells (HPMCs) cultured with amino acid-based PDF resulted in higher IL-6 secretion, indicative of improved synthetic capacity of the cells.¹⁵

In our *in vivo* study we found that the glucose concentration of the CAPD solution has no effect on basal IL-6 and TNF- α levels of peritoneal fluid. There is no similar study in the literature concerning effects of different glucose concentrations on spent dialysate cytokine concentrations. How can these contrary *in vitro* and *in vivo* results for the effect of glucose concentration on unstimulated IL-6 and TNF- α levels in spent dialysate be explained? First, *in vivo* results are affected by the whole biologic milieu and may be substantially different from the *in vitro* systems that characteristically under the insult of multiple factors. Lactate or another factor may hinder the effect of different glucose concentrations on cytokine release; also, a type 2 statistical error cannot be excluded.

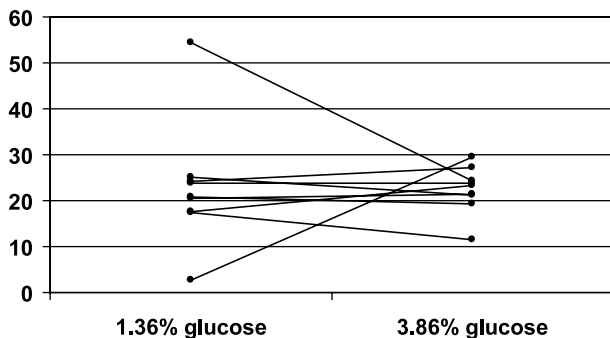


FIG. 1. TNF- α levels after 1.36% and 3.86% glucose used dwells for each patient.

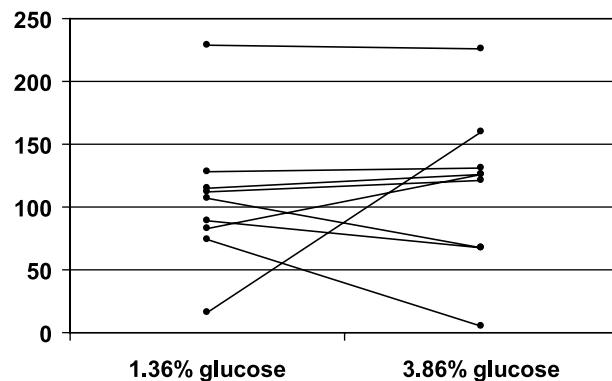


FIG. 2. IL-6 levels after 1.36% and 3.86% glucose used dwells for each patient.

In conclusion, in CAPD patients conventional lactate-based PDF glucose concentration does not seem to effect the peritoneal release of IL-6 and TNF- α *in vivo*. Further *in vivo* studies are needed with non-lactate-based solutions in order to determine the effect of glucose concentration *per se* on peritoneal cytokine release.

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