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1,3-ß-D-Glucan testing is highly specific in patients undergoing dialysis treatment

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Summary *Background:* The aim of this combined in-vitro and in-vivo study was to investigate whether state of the art dialysis modalities produce false positive serum 1,3-ß-D-Glucan (BDG) levels.
Methods: Dialysis fluid for simulated dialysis treatments was spiked with BDG from different sources. Samples were taken from the dialysate and dialyzer blood compartments at various time points. In addition, serum samples were obtained in three groups of patients without invasive fungal disease: a.) twelve patients on chronic hemodialysis (HD)/hemodiafiltration (HDF); b.) ten patients on continuous ambulatory peritoneal dialysis (CAPD); and c.) ten patients with stable chronic kidney disease (CKD) but without dialysis.
Results: Median BDG levels in BDG spiked dialysate were 3250.9, 2050.4, and 390.1 pg/ml respectively. All corresponding samples from the blood compartments were BDG negative.

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In HD/HDF patients no increase of serum BDG levels could be observed over the duration of treatment. 71/72 BDG tests in this group remained negative. BDG tests were also negative in 9/10 CAPD patients, both in in- and outflow dialysates as well as in all ten patients with CKD.
Conclusion: We conclude that state of the art renal replacement therapies using up-to-date treatments are not a cause of falsely elevated serum BDG levels.

Introduction

Positive testing for 1,3-ß-D-Glucan (BDG) in serum is widely used to assess invasive fungal infections (IFIs).[1–4] It detects circulating BDG, which is part of the fungal cell wall of most clinical relevant fungi such as *Candida* spp. and *Aspergillus* spp. and which are also ubiquitously found in the clinical environment. However, a large number of medical devices and drugs have been associated with falsely elevated BDG levels because of cellulose, the 1,4-β-glycosidic isomer to BDG. Cellulose is a structural component in surgical gauzes and filters and is used in the manufacturing process of intravenous medication such as antibiotics and albumin.[5–9] Additionally, extracorporeal blood purification methods were blamed to elevate BDG levels even in absence of IFIs.[2,10–18] The source for a low positive predictive value of BDG testing in presence of hemodialysis (HD) or hemodiafiltration (HDF) has been ascribed to the use of cellulose based membranes (cuprophane) in the early days of dialysis and leaching of BDG or BDG-like moieties from such membranes in absence of IFIs. While contributing to the early success of HD, cellulose membranes are no longer used for reasons of limited biocompatibility.[19–21] Today, dialysis membranes are produced from artificial polymers, mostly polysulfone, or chemically modified cellulose such as cellulose acetate, which no longer release or leach BDG or BDG-like moieties. Only few studies reported on BDG performance in patients with ongoing HD/HDF using synthetic membranes.[22] Results are contradictory and more detailed information regarding HD/HDF modalities is often lacking, so that reliable conclusions regarding BDG performance in patients undergoing dialysis treatment remains inconclusive.

Certainty about the performance and reliability of BDG testing in patients with ongoing dialysis treatment is of utmost interest, as survival rate with IFI importantly depends on rapid initiation of appropriate antifungal therapy.[23,24] Dialysis dependent patients are considered a vulnerable cohort for IFI development. In a case—control study among 350 patients with candidemia, 78 episodes (22%) occurred in patients with HD, and HD was an independent risk factor for developing candidemia in that study.[25] As both, IFIs (e.g. candidemia)[26] and acute kidney injury requiring dialysis therapy are frequent events in critically ill patients treated in intensive care units,[27] certainty about BDG performance for early IFI diagnosis in this vulnerable cohort of patients is of utmost importance.

The aim of this combined in-vitro and in-vivo study therefore was to clarify whether current dialysis modalities such as HD/HDF using a standard non-cellulosic dialyzer-membrane and delivering ultra-pure dialysate can be excluded as a source for BDG contamination, and whether such a membrane prevents leaking of dialysate spiked with high concentrations of BDG. For this purpose we performed lab bench experiments using an artificial dialysis model and investigated BDG test performance in patients with different types of dialysis treatments and pre-dialysis chronic kidney disease stages. Additionally, HD, HDF, and CAPD were investigated as potential source for false positive BDG values in patients with ongoing dialysis treatment.

Methods

This prospective study was conducted between March 2015 and March 2016 at the Department of Internal Medicine and the Institute of Physiology, both Medical University of Graz, Graz, Austria. To clarify the role of BDG testing in dialysis patients we performed lab bench studies using BDG spiked dialysate and investigated whether BDG may pass from the dialysate through the membrane to the blood side. We additionally measured BDG levels in patients without evidence of IFIs undergoing different types of dialysis due to chronic renal failure and in stable chronic kidney disease (CKD) without renal replacement therapy (RRT).

Lab bench study

Lab bench studies were done using standard dialysis equipment, a 4008H hemodialysis machine (Fresenius Medical Care, FMC, Schweinfurt, Germany) equipped with polysulfone filters (Diasafe®, FMC) for on-line preparation and delivery of ultra-pure dialysate from reverse osmosis water,[28,29] solid sodium bicarbonate (BiBag, FMC) and liquid acid concentrates (SW240A, B Braun, Melsungen, Germany), standard blood lines, and a standard high-flux dialyzer (Polyflux 210H, Gambro AB, Hechingen, Germany). Prior to each experiment the machine and the dialysate flow-path was heat-disinfected by the machine's in-built cleaning program using hot citric acid. Leaching and contamination experiments were conducted for a duration of 4 h simulating usual dialysis operating conditions. Flows through dialyzer blood (Qb) and dialysate (Qd) compartments were set to 300 and 500 mL/min, respectively. Studies were done in hemodialysis mode without ultrafiltration, dialysate conductivities were set at 14 mS/cm and dialysate temperature was set at 37 °C. In the leaching and contamination experiments a batch of dialysate loaded with BDG was recirculated through the dialysate compartment using a 5 L reservoir (Fig. 1). The blood compartment was perfused by fresh dialysate produced by the dialysis machine in a single-pass setup, while the dialysate compartment was perfused by dialysate spiked with BDG (produced or purchased as described below) (Fig. 1). Samples were taken at baseline (0) and in hourly intervals[1–4]