Letter to the Editor

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Effect of Dialysate Buffer on Serum Beta-2-Microglobulin Levels in Chronic Hemodialysis

Dear Sir,

In patients with end-stage renal disease dialysis-related amyloidosis (DRA), also termed AB-amyloidosis referring to its precursor protein β_2-microglobulin (β2m), has been identified as an important cause of morbidity. The pathogenesis of DRA remains largely obscure. Uremia is undoubtedly a major precondition for this disorder, but non-transplant renal replacement therapy also affects precipitation of the disease. The pathophysiological process underlying amyloidogenesis cannot be explained solely on the basis of simple retention and deposition of amyloid, but may also involve cell activation and generation of inflammatory mediators which consequently alter processing of β2m and favor its osteoarticular deposition [1].

There is growing evidence that the bioincompatibility of maintenance hemodialysis procedures is important in the pathogenesis of DRA. Cuprophane dialysis membranes are known to activate complement and cells, to cause increased production of β2m and to augment uremic β2m body burden [2]. On the other hand highly permeable and biocompatible membranes eliminate β2m, reduce circulating β2m concentrations [3] and postpone the development of the major clinical manifestations of DRA [4]. In addition, use of ultrapure dialysate has been shown to lower the incidence of the ensuing carpal tunnel syndrome [5]. The question, whether or not the chemical composition of the dialysate affects the pathogenesis of DRA, has not been investigated in clinical studies. The present prospective, randomized comparison was aimed to elucidate the effect of different dialysate buffers on circulating β2m concentrations in patients undergoing maintenance hemodialysis. Forty-one stable chronic hemodialysis patients with end-stage renal disease of different etiologies, maintained on acetate hemodialysis utilizing the low-flux cellulose acetate membrane for at least 2 years, were randomly assigned to 4 study groups: group A continued hemodialysis on acetate dialysate and cellulose acetate membranes (FB130, surface area 1.3 m^2, Baxter, Ill., USA); group B remained on acetate dialysate but changed to a high flux polysulfone membrane (F60, surface area 1.25 m^2, Fresenius, Oberursel, Germany); group C changed to bicarbonate dialysate but remained on a low-flux cellulose acetate membrane, and group D was treated with bicarbonate dialysate and a high-flux polysulfone membrane. Hemodialysis was performed three times a week for 4–5 h (MTS A 2008 C delivery system, Fresenius); nominal dialysate flow rate was 500 ml/min, blood flow rates ranged from 200 to 250 ml/min, fluid removal rate was adjusted to clinical needs. The chemical composition of the dialysates used were identical in terms of calcium, magnesium, and glucose concentration, but contained either acetate (35 mmol/l) or bicarbonate (32 mmol/l). The sodium and potassium concentrations were adjusted to the patient's values. Throughout the study the individual hemodialysis regime remained unchanged. Serum levels of β2m were determined using routine laboratory methods.

There were no statistically significant differences in the demographic characteristics of the 4 groups of anuric patients at recruitment (table 1). Circulating β2m levels were markedly elevated in all patients at baseline, but they took different courses during the study period of 1 year follow-up. Continuation of the previous regimen of acetate dialysate and cellulose acetate membrane resulted in constant β2m levels. The introduction of high-flux polysulfone membranes to patients receiving acetate dialysis caused a significant reduction in serum β2m. A more pronounced fall in serum β2m was noted in patients treated with polysulfone membranes. However, by comparison with patients receiving bicarbonate dialysis, patients treated with acetate dialysates had significantly higher serum β2m levels (table 2).

Our investigation demonstrates that the choice of dialysate buffer affects circulating β2m levels independent of the biocompatibility and permeability of the dialyzer membrane used. The previously published notion that exposure of patient's blood to acetate dialysate for 1 or 6 weeks resulted in elevated serum β2m concentrations [6] is confirmed and extended by our data. Higher circulating β2m levels in response to acetate dialysate may be explained at least by two different causes. Under the condition of hemodialysis these mechanisms may not operate separate-

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Table 1. Characteristics of patients at recruitment

Group	Membrane	Dialysate buffer	Number (f/m)	Age,years (range)	Time on HD[1] months (range)	Urine volume[1] ml/day (range)
A	CA	acetate	9 (6/3)	50.3 (29–72)	43.7 ± 13.8 (26–62)	52.2 ± 35.2 (0–100)
B	CA	bicarbonate	10 (6/4)	51.8 (35–66)	43.3 ± 15.4 (26–72)	23.6 ± 33.3 (0–100)
C	PS	acetate	11 (6/5)	52.4 (28–71)	40.5 ± 19.8 (19–81)	36.4 ± 37.5 (0–100)
D	PS	bicarbonate	11 (7/4)	52.8 (36–66)	39.7 ± 11.8 (19–56)	27.3 ± 40.0 (0–100)

CA = Cellulose acetate; PS = polysulfone; HD = hemodialysis.
[1] Mean ± SD.

Table 2. Serum β2m levels (mean b SD) in the 4 treatment groups: effects of porosity of dialysis membrane and of dialysate buffer

Group	Membrane	Dialysate buffer	Serum β2m levels, mg/l		
			0 months	6 months	12 months
A	CA	acetate	50.2 ± 7.5	51.6 ± 5.8	51.7 ± 5.8
B	CA	bicarbonate	49.8 ± 8.7	46.5 ± 7.3	46.2 ± 9.9*
C	PS	acetate	50.1 ± 8.5	39.2 ± 6.5	41.6 ± 8.5
D	PS	bicarbonate	48.8 ± 7.9	33.5 ± 6.9	31.7 ± 7.2*

CA = Cellulose acetate; PS = polysulfone.
* $p < 0.05$ vs. corresponding values of patients on acetate dialysate.

ly but synergistically. First, Sonikian et al. [6] performed in vitro and in vivo studies indicating that metabolic acidosis enhances β2m generation and release. Secondly, acetate may exert a direct effect on monocytes or lymphocytes or may induce the liberation of inflammatory mediators such as cytokines or growth factors, which stimulate β2m synthesis by these cells [7–10].

Our observations have clinical implications, because at present there is no causal therapy for established DRA. It would be prudent to recommend the use of highly permeable, biocompatible dialyzer membranes in combination with sterile bicarbonate dialysate to postpone DRA in those patients at increased risk of this disorder: namely all patients who have no chance of receiving a kidney transplant and patients over 55 years.

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