Revisiting the Role of Flux in β_2 -Microglobulin Removal

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β_2 -Microglobulin is the light chain complex of the major histocompatibility complex (MHC) class 1 molecule which is synthesized by all cells that express such molecules. Once shed from the cell surface, β_2 -microglobulin disassociates and enters the circulation as a monomer with a molecular weight of 11,815 Da. In normal subjects it is cleared by the human kidney where it is freely filtered and almost fully adsorbed and catabolized by proximal tubular cells. In patients with impaired renal function plasma levels are elevated and removal by dialytic techniques is highly dependent upon convection.

β_2 -Microglobulin is widely recognized as a key component in the genesis and development of dialysis-associated amyloidosis, a syndrome that is clinically expressed in terms of destructive arthropathies and carpal tunnel syndrome [1].

The mechanisms whereby β_2 -microglobulin mediates osteoarticular amyloidosis remain incompletely understood; chemotaxis, activation of monocytes and macrophages with subsequent release of cytokines and metalloproteinases secondary to the modification of β_2 -microglobulin by advanced glycation end products are pivotal as is the formation of amyloid fibrils arising from the binding of β_2 -microglobulin to collagen [2–4].

Although no firm relationship exists between plasma β_2 -microglobulin concentrations and the degree of severity of dialysis-associated amyloidosis [5], observational studies have demonstrated that the use of high-flux hemodialysis and convective therapies such as hemofiltration

and hemodiafiltration, reduce plasma β_2 -microglobulin concentrations, and their use is associated with a lower incidence of treatment-related amyloidosis. Nevertheless it is highly probable that residual renal function is probably the most important determinant of plasma β_2 -microglobulin levels in hemodialysis patients and removal via this route even with minimal renal function may supersede enhanced convective clearance [6]. Despite this, considerable effort has been placed into the improvement of membrane permeability to β_2 -microglobulin over recent years [7]. Additionally the kinetics of β_2 -microglobulin removal are thought to be generalizable and representative of the kinetic behavior of other middle molecules prompting its use as a general marker for middle molecules by European Best Practice Guidelines for Haemodialysis [8].

In the study by Traut and colleagues [10], the topic of β_2 -microglobulin removal has been revisited and their study has confirmed that patients treated using high-flux polyamide membranes have lower plasma β_2 -microglobulin levels compared with patients treated using low-flux cellulose-based membranes. Their observation that, in common with normal controls, significantly higher amounts of β_2 -microglobulin were bound to the cells of patients undergoing dialytic treatment with high-flux membranes compared to patients treated with low-flux membranes is of considerable interest. Additionally, Traut and colleagues also noted that more β_2 -microglobulin was released from the cells during dialysis with low-

flux membranes, and postulated that this contributed to plasma concentrations owing to the limited removal capacity of low-flux membranes.

Although the authors have not provided any information on binding sites, their observations are suggestive of the existence of functional differences between cells in patients being treated with high-flux membranes compared to those treated with low-flux membranes. This is not a novel observation and a number of factors may contribute to such differences, the interaction between blood and the membrane during dialysis, which results in the activation of not only the immune but also the cellular systems of the body, the greater range of uremic solute removal by high-flux compared to low-flux membranes. Dialysis membranes are semi-permeable and nonselective, and endotoxin fragments have been shown to stimulate β_2 -microglobulin synthesis. Whilst the current stud-

ies were undertaken using high-quality water in which there were no colony-forming units in the water and whose endotoxin content was <0.01 EU/ml, the presence of DNA fragments and their passage across the membrane during dialysis cannot be totally discounted [9].

The similarity in the amount of β_2 -microglobulin bound to the leukocytes of patients treated with high-flux membranes to those of the normal subject is suggestive of high-flux dialysis partially normalizing the uremic milieu within which the cells exist. Further studies are required to establish if this in fact is the case and/or to identify the reason(s) responsible for this difference. The incubation of normal cells with samples of ultrafiltrate collected from patients undergoing dialysis with low-flux and high-flux membranes would seem to be the natural first stage in this process.

References

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