

SECTION FIVE:

Amyloidosis

Increased beta-2 microglobulin levels are associated with increased risk of mortality, and its accumulation leads to a form of amyloidosis. The debilitating effects of amyloidosis, such as carpal tunnel syndrome and arthropathies, impact a large percentage of dialysis patients, particularly as the number of years on therapy increases. Daily dialysis removes beta-2 microglobulin more efficiently, potentially delaying or preventing the progression of amyloid disease.

INTRODUCTION

Beta-2 microglobulin (B2M) is a relatively large molecule (a small protein), and it has been estimated that 150-200 mg of B2M are synthesized daily.⁸⁴ Healthy kidneys efficiently remove excess amounts of B2M from the blood. However, B2M tends to accumulate in long-term hemodialysis patients because its large size hinders effective diffusion across standard hemodialysis membranes.

Elevated blood levels of B2M have been linked to the development of various connective tissue disorders. B2M precipitates to form fibrillar amyloid-like structures in these tissues and this causes a form of amyloidosis—one of the most painful and disabling complications of ESRD. Effects may include carpal tunnel syndrome (CTS), peripheral arthropathy, spondyloarthropathy, and other severe arthropathies.

Duration on dialysis is a known risk factor for amyloidosis. One study reported that the prevalence of amyloidosis was 20% after 2 years and increased to 100% in patients treated for more than 13 years with hemodialysis.⁸⁴ Up to one third of maintenance dialysis patients suffer from CTS⁸⁴ and prevalence increases with dialysis vintage, with nearly all patients having CTS after 13 to 20 years of dialysis. Arthralgias may be manifested as shoulder pain and stiffness after 5 years of dialysis; the incidence of dialysis-related arthralgias increases to affect as many as 50% of patients by 13 years of conventional hemodialysis. Symptoms tend to worsen over time and the joint may become immobile.

In the NIH-sponsored HEMO study, a 1846- patient randomized clinical trial, serum B2M levels were identified as an independent mortality predictor. Each incremental increase of 10 mg/L of serum B2M increases relative risk of mortality by 13%.⁸⁵

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Current dialysis regimens do not adequately remove B2M. Several studies have documented increases in B2M serum levels in chronic kidney failure As with phosphorous (see section on Hyperphosphatemia), B2M does not rapidly exchange between body compartments. Serum B2M levels may decrease during treatment, but rise significantly following treatment.⁸⁴ In addition, traditional dialysis membranes become less efficient in removal of B2M during the course of therapy due to protein coating and reduced sieving capabilities for a molecule as large as B2M.

There is some evidence that amyloidosis develops more slowly in patients dialyzed with high flux biocompatible membranes and/or convective therapies, but weekly patient generation of B2M exceeds removal⁸⁴ in conventional therapy schedules. Chronic inflammation induced by bioincompatible membranes and/or non-sterile fluids may stimulate the synthesis of B2M, exacerbating the issue.⁸⁴

POTENTIAL BENEFITS OF DAILY THERAPY

By increasing therapy frequency and/or duration, additional B2M reduction may be achieved, because of the lessened impact of post-treatment rebound and because of the potential for increased dialyzer membrane efficiency. This may delay and/or prevent the onset and progression of debilitating amyloid.

SUMMARY OF PUBLISHED RESULTS

Both nocturnal (NHD) and daily (SHD) renal replacement therapy remove B2M more effectively than conventional thrice-weekly hemodialysis, although nocturnal therapy may have an advantage.

- B2M serum levels were reduced by 20% to 49% by daily treatment as compared to conventional dialysis.^{22, 56, 83, 86-88}
- Over 1 week, 3.89 to 4.6 times as much B2M was removed by NHD^{58, 69, 86} and 1.4 times as much was removed by SHD.⁸⁹

TABULATED STUDY FINDINGS ON AMYLOIDOSIS

| Study & Design | Supporting Points |
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| <p>Jaber, BL. Blood Purif. 2004; 22:481⁵⁴</p> <p>Daily HF 12 pts; 4 wk Prospective</p> | <ul style="list-style-type: none"> • Median B2M removal/session was 170 mg. • B2M decreased from 48 ± 34 mg/L on conventional dialysis to 36 ± 25 mg/dL ($p < 0.07$) |
| <p>Kawanishi, H. Blood Purif. 2004; 22(Suppl. 2):8⁹⁰</p> <p>Daily HF 6pts; 7 wk Prospective</p> | <ul style="list-style-type: none"> • B2M decreased significantly from 25.4 ± 2.6 mg/L to 20.1 ± 2.9 mg/L |
| <p>Williams, AW. Am J Kid Dis. 2004; 43:90⁵³</p> <p>Daily HD 20 pts; 4 wk Prospective</p> | <ul style="list-style-type: none"> • After 4 weeks, there was no significant change in plasma B2M levels |
| <p>Luders, C. J Am Soc Nephrol. 2003; 14:F-PO678⁹¹</p> <p>Daily HD 15 pts; 1 yr Prospective</p> | <ul style="list-style-type: none"> • Serum B2M levels declined significantly during daily HD from 28 ± 10 mg/L before daily HD to 22 ± 6 mg/L after 1 year of daily HD ($p < 0.01$) |
| <p>Maduell, F. Kidney Int. 2003; 64:305²⁰</p> <p>Daily HDF 8 pts; 6 mo Prospective</p> | <ul style="list-style-type: none"> • Mean serum B2M decreased from 29.5 mg/L on conventional HDF to about 24 mg/L on daily HDF ($p < 0.01$) • Increase in the weekly percentage removal of B2M was 67% |
| <p>Zimmerman, DL. ASAIO Journal. 2003; 49:426⁶⁶</p> <p>Daily HF 11 pts; 4 wk</p> | <ul style="list-style-type: none"> • Serum levels of B2M were 19.2 ± 5.52 mg/L on daily hemofiltration and 22.88 ± 5.25 mg/L on conventional hemodialysis ($p = 0.06$) |

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| <p>Floridi, A. Nephrol Dial Transplant. 2002; 17:871⁸⁸</p> <p>Daily HD 32 pts; 6 mo Prospective</p> | <ul style="list-style-type: none"> • Plasma glycation products (furosine, protein-bound and free pentosidine, and low molecular mass AGE peptides) were significantly lower in patients on daily hemodialysis compared to those on conventional hemodialysis. Concentrations of these AGEs were 19-56% less in the daily HD patients ($p < 0.05$) • Plasma levels of AGEs were much higher in all dialysis patients than in healthy controls and in patients with chronic renal failure who were not yet on dialysis |
| <p>Fagugli, RM. Int J Artifc Org. 2001;24:256⁸³</p> <p>Daily HD 10 pts; 1 yr (6 mo random crossover)</p> | <ul style="list-style-type: none"> • Fluorescence from AGEs in serum was significantly lower during 6 months of daily HD than during a crossover period of 6 months of conventional HD: 201.3 ± 36.4 AU/ml vs. 267.5 ± 141.4 AU/ml ($p = 0.03$) |
| <p>Galland, R. J Am Soc Nephrol. 2001;12:266A⁸⁹</p> <p>Daily HD, DHF 1 pt; 3 wk on each</p> | <ul style="list-style-type: none"> • Removal of B2M was 648 mg/week by daily HF, 440 mg/week by daily HD, 318 mg by conventional HD |
| <p>Traeger, J. Dial Transplant. 2001;30:76²²</p> <p>Daily HD 15 pts; 1 yr or more Prospective</p> | <ul style="list-style-type: none"> • B2M decreased from 34.6 ± 10.3 mg/dL to 24.8 ± 11.5 mg/dL ($p < 0.05$) |
| <p>Raj, DSC. Nephrol Dial Transplant. 2000;15:58⁸⁶</p> <p>Nocturnal HD 10 pts; 9 mo Prospective</p> | <ul style="list-style-type: none"> • Pre-dialysis B2M levels decreased from 27.2 ± 8.1 mg/dL on conventional HD to 13.7 ± 4.4 mg/dL on nocturnal HD ($p < 0.0001$) • Mass of B2M removed by nocturnal HD was 585.2 ± 309.2 mg compared to 127.4 ± 48.7 mg by conventional HD ($p < 0.001$); this was a $38.8\% \pm 7.1\%$ reduction in serum levels by nocturnal HD vs. a $20.5\% \pm 5.8\%$ reduction by conventional HD ($p < 0.0001$) |
| <p>O'Sullivan, DA. Mayo Clin Proc. 1998;73:1035⁵⁶</p> <p>Nocturnal HD 5 pts; 8 wk Prospective</p> | <ul style="list-style-type: none"> • B2M levels were 27.1 ± 4.72 mg/L on conventional HD and 21.7 ± 4.48 mg/L during nocturnal HD ($p < 0.062$) |

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| <p>Pierratos, A. J Am Soc Nephrol. 1998;9:859 ⁶⁹</p> <p>Nocturnal HD 11 pts; 3 yr Prospective</p> | <ul style="list-style-type: none"> • Weekly removal of B2M by nocturnal HD was about 4 times that by conventional HD • Serum B2M levels decreased from about 2.4 mmol/L to about 1.4 mmol/L |
| <p>Kubo, S. Nephron. 1996;72:93 ⁸⁷</p> <p>Daily HD 1 pt; 10 wk Case-control</p> | <ul style="list-style-type: none"> • B2M levels were 32.4 ± 2.8 mg/L during conventional HD and 18.7 ± 1.3 mg/L during daily HD (no p value given) |
| <p>Uldall, R. Adv Ren Repl Therap. 1996;3:133 ⁵⁸</p> <p>Nocturnal HD 5 pts; 6-16 mo Prospective</p> | <ul style="list-style-type: none"> • B2M removal was much greater with nocturnal HD (657 mg/week) compared to conventional HD (173 mg/week) |

