

Beta-2 Microglobulin Amyloidosis: Past, Present, and Future

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Abstract

Almost half a century has elapsed since the first description of dialysis-related amyloidosis (DRA), a disorder caused by excessive accumulation of β -2 microglobulin (B2M). Within that period, substantial advances in RRT occurred. These improvements have led to a decrease in the incidence of DRA. In many countries, DRA is considered a “disappearing act” or complication. Although the prevalence of patients living with RRT increases, not all will have access to kidney transplantation. Consequently, the number of patients requiring interventions for treatment of DRA is postulated to increase. This postulate has been borne out in Japan, where the number of patients with ESKD requiring surgery for carpal tunnel continues to increase. Clinicians treating patients with ESKD have treatment options to improve B2M clearance; however, there is a need to identify ways to translate improved B2M clearance into improved quality of life for patients undergoing long-term dialysis.

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Introduction

More than 79 years after the first patient was successfully treated with hemodialysis (HD), the prevalence of patients living with ESKD continues to increase worldwide (1). Unfortunately, not all individuals will be candidates for kidney transplantation, and those who remain on long-term HD may survive for decades. Although there have been technical advances in dialysis over time, living with ESKD inevitably results in accumulation of pathogenic substances (2).

In 1975, an increased incidence of carpal tunnel syndrome (CTS) in patients on long-term HD was documented (3). The etiopathogenesis was postulated to arise from high venous pressures in Cimino–Brescia HD fistulas that produced wrist edema with consequent median nerve compression (4). This hypothesis remained prevalent until the early 1980s, but was abandoned after cases of bilateral CTS demonstrated independence from arteriovenous vascular access (5).

Subsequently, multiple investigators analyzed surgical samples from patients on HD who had undergone CTS surgery, and they discovered brownish synovial deposits in the synovium. Microscopic analysis revealed Congo-Red staining, characteristic of amyloid (6). Secondary amyloidosis from plasma-cell dyscrasias or chronic infections that are responsible for amyloid light-chain and amyloid A amyloidosis, respectively, were absent. Accordingly, a different form of amyloid, unique to kidney failure, was postulated.

Several years later, analysis of synovial amyloid resulted in the discovery of β -2 microglobulin (B2M), a 12,000-D molecule (7). Similar deposits were found in biopsy specimens of rectal mucosa from some of these

patients, expanding the view of this disease as a systemic process produced by B2M accumulation (8). B2M amyloid fibers involve almost every organ, except the brain, leading to a variety of clinical entities described as “dialysis-related amyloidosis” (DRA) (9).

Epidemiology and Risk Factors

Risk factors for DRA include older age, greater dialysis vintage, low-flux or bioincompatible dialysis membrane use, and absent or minimal residual renal function (10,11). The prevalence of DRA in patients on peritoneal dialysis is estimated to be similar to patients on HD, perhaps due to a balance of risk factors, such as less clearance with peritoneal dialysis of B2M, but increased residual renal function in this population (12,13).

Histologic evidence of DRA was nearly a universal finding in patients on long-term dialysis (>10 years) (14). However, the epidemiology of DRA evolved with a decrease in symptom frequency, especially during the initial decade of dialysis (15). This decline is likely a consequence of the use of high-flux membranes (16) that have superior B2M clearance, ultra-purified water, and more biocompatible membranes that generate less of an inflammatory response, as compared with older membranes (17,18).

The most dramatic demonstration of the decrease in DRA frequency is the study by Schwalbe *et al.* (17). Here, the prevalence of DRA by clinical and radiologic parameters decreased by 80% from 1988 to 1996. CTS was diagnosed in seven of 43 patients in 1988, but in only one of 43 in 1996. Consequently, DRA was considered to be a disappearing entity. More recent data

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reveal that DRA remains an important complication of longer time on dialysis (Figure 1, Table 1). In the last 10 years, one Japanese and one German study found that nearly 20% of patients had evidence of DRA, with a significant proportion requiring surgical intervention (15,19). More recently, a population-based study from Taiwan, which included 17,000 patients, reflected a 10-year cumulative incidence of CTS in patients on dialysis of 8% versus 5% in matched individuals who were not on dialysis (20). Patients with CTS in the dialyzed group were more likely to receive surgical intervention than those in the control group (62% versus 13%), implying more advanced and symptomatic disease in the dialyzed group. Importantly, the number of patients living with ESKD has increased as the population with risk factors (such as diabetes) has expanded (21). Consequently, the absolute number of patients requiring interventions for DRA complications has risen in some places (22).

Pathophysiology

Before the discovery of B2M as an amyloidogenic molecule, proteolytic cleavage of native protein was considered essential to amyloid formation (23). However, after the amyloid of patients on dialysis was determined to have a similar molecular mass as intact B2M, and x-ray crystallography demonstrated that almost half of the amino acid residues of B2M participated in the characteristic β -pleated-sheet formation of amyloid, the origin of B2M was essentially confirmed (24,25).

To understand how and to what extent B2M accumulates in CKD, normal B2M production (as the β chain of class I

human leukocyte antigen molecules) and elimination are reviewed (26). B2M is produced at a rate of 0.159 mg/hr per kilogram body weight (approximately 200–300 mg/d) (27). B2M, shed into the circulation, undergoes glomerular filtration with subsequent near-total uptake by the proximal tubule receptor megalin and consequent catabolism to amino acids (Figure 2). Only about 1% of B2M elimination is extrarenal. The result of the above is a normal B2M plasma concentration of 1.5–3 mg/L. As glomerular filtration declines, serum levels increase. In ESKD, B2M levels are generally in the range of 25–35 mg/L. Inflammation, acidosis, and exposure to bioincompatible dialysis membranes (among other influences) can increase B2M levels (28).

Hemodialytic clearance is a function of dialysis time and technique. Standard HD sessions provide only partial clearance of B2M. For example, high-flux HD, conducted for 4 hours thrice weekly, clears 1.32 mg/kg per session. In a 70-kg patient, the annual B2M retention by high-flux membranes is approximately 73 g, in contrast to 111 g with a low-flux membrane (26). This one-third increase in B2M clearance plausibly explains why the dramatic reduction in DRA occurred after the late 1980s, *i.e.*, due to the use of high-flux membranes (29).

In vitro, investigations have demonstrated amyloid-fiber formation from concentrated samples obtained from carpal synovial tissue of patients on HD (23), suggesting that elevated concentrations of B2M led to amyloid formation. Conversely, Zhang *et al.* (30) rendered a different conclusion regarding the role of high B2M levels in amyloidogenesis. In an animal model, using B2M concentrations at four-fold higher concentrations than in plasma from patients on HD, spontaneous fibrillogenesis failed to occur, implying that

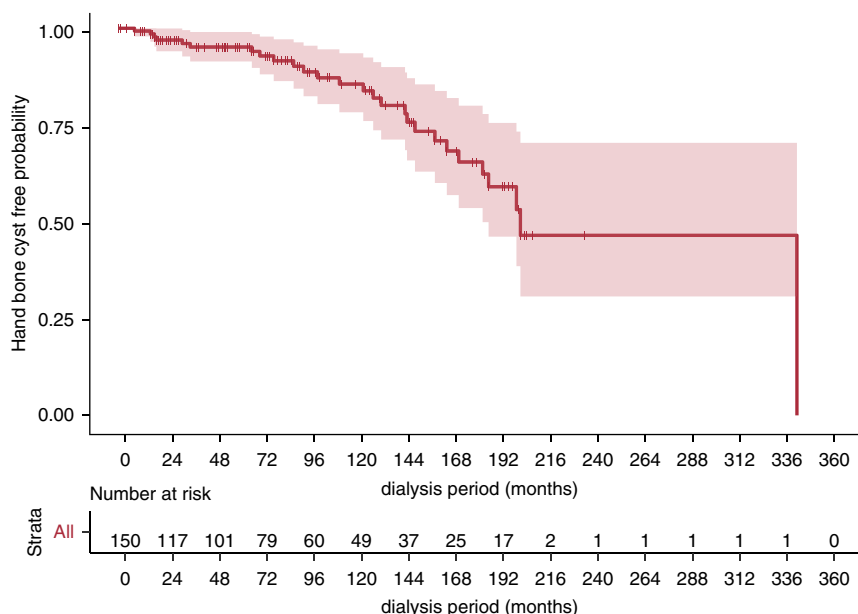


Figure 1. | Development of hand bone cyst from β 2 microglobulin amyloidosis increased between 2006 and 2013 in a Japanese hemodialysis facility. Cyst probability (red solid line; 1 represents cyst-free probability) is shown for 150 subjects with respective time on hemodialysis (95% confidence intervals are represented by shaded regions). Generally, dialysis was conducted thrice weekly for 5 hours at blood flow rates of 200–250 ml/min with biocompatible membranes. Bone radiographs were obtained yearly from 2006 to 2013. Point prevalence is calculated by multiplying number of subjects at risk. Cyst probability increased gradually over 72 months, with an accelerated probability afterward. Note that some patients already had hand bone cyst(s) in the first year of survey, thus the exact time of occurrence might be earlier than illustrated.

Table 1. Clinical manifestations of dialysis-related amyloidosis

Anatomic Location	Prevalence after 10 Yr of Hemodialysis	Clinical Manifestations	Diagnostic Clues
Carpal tunnel syndrome	10%–20% (15)	Hand pain, paresthesias, grip weakness	Bilateral manifestations in patients on dialysis
Tendons	15% (53)	Tendinitis: shoulder pain, stiffness, trigger finger	Ultrasound or MRI findings of thickened supraspinous or subscapularis tendons, with lesser involvement of infraspinatus or teres minor tendons
Spine	20%	DSA: back pain, neck pain, radicular pain, cord compression	Findings by conventional radiography or CT of narrowing of intervertebral spaces, severe bone erosions, cysts, and end-plate destruction without significant amount of osteophyte formation
Gastrointestinal	>30% of patients with evidence of DRA ^a (9,70)	Pseudo-obstruction, bleeding, ischemia	
Cardiac	Uncommon ^b (16)	Heart failure, hypotension	

Prevalence of dialysis-related amyloidosis increases with dialysis vintage. MRI, magnetic resonance imaging; DSA, destructive spondyloarthropathy; CT, computed tomography; DRA, dialysis-related amyloidosis.
^aPrevalence of gastrointestinal amyloidosis was derived mainly from histologic samples of patients exposed to older hemodialytic therapies who had no gastrointestinal complications.
^bPrevalence: Exact calculation of prevalence is not possible and depends on a number of risk factors that increase with dialysis vintage. Symptomatic disease is uncommon before 10 yr of dialysis vintage. Diagnosis: The gold standard is histopathologic demonstration of amyloidosis formation.

elevated B2M concentrations alone were insufficient to produce amyloid (30). A separate observation—in which a mutant, thermodynamically unstable, B2M variant produced amyloid at normal serum levels of B2M (31)—lent further credence to the notion that other permissive factors of fibrillogenesis, aside from elevated B2M concentrations, were required. Furthermore, although abnormally high serum levels of B2M are a prerequisite to amyloidogenesis, additional increases in plasma levels do not correlate with the risk of DRA (32).

The formation of amyloid fibers follows a classic nucleation-polymerization model in which a thermodynamically unfavorable nucleation reaction becomes favorable once a stable nucleus is formed (33,34). High, local B2M concentrations at an optimum pH of 2–3, or stabilization of B2M molecules, favors nucleation (35). Notably, this optimum pH is far lower than that encountered in human physiology (36); however, polymerization of fibrils at physiologic pH might be supported by ApoE, proteoglycans, glycosaminoglycans, type-1 collagen, nonesterified fatty acid, and lysophospholipids (37,38). Several of the latter molecules reside in synovia, which may partially account for the affinity of amyloid for osteoarticular surfaces. Amyloid formation starts in the cartilage, subsequently invading the synovium, and lastly the bone (39). Previously, HD was carried out with the copper-exposed Cuprophan dialyzer membranes, which have been in disuse for more than three decades. Because copper is known to destabilize the native conformation of B2M, thereby promoting fibril formation, we can now retrospectively speculate that the previously greater frequency of DRA was at least partially attributable to the composition of these now-defunct membranes (40).

Post-translational modification and advanced glycation end products (AGEs) likely participate in B2M amyloidogenesis (41). AGE-modified B2M can interact with synovial fibroblasts that express AGE receptors (42,43), with consequent generation of monocyte chemoattractant peptide-1 and monocyte chemotaxis to the locus of amyloid creation (Figure 2, Table 2) (44). B2M-exposed macrophages may then produce proinflammatory cytokines and regulatory cytokines such as the TGF- β (45). Conversely, unmodified B2M interacts with collagen and fibroblasts, and increases secretion of matrix metalloproteinase-3, which has broad capability for cartilaginous degradation (46,47). The putative differential responses to modified or unmodified B2M were further characterized *in vitro*. Fibroblasts endocytosed modified B2M, but unmodified B2M remained near the plasma membrane (48), thus, presumably, not leading to the transcription of genes involved in inflammation. Overall, the net effect of tissue-embedded, modified B2M is an enhanced and destructive inflammatory state that involves synovium and surrounding tissues (49).

Clinical Manifestations

The earliest evidence of DRA was documented from histologic samples, beginning about 2 years after initiation of HD. Symptoms due to amyloid deposition typically present after a dialysis vintage of at least 5 years (50). With 30 years of HD, the majority of patients required surgical intervention for complications of DRA (51), of which the clinical spectrum is extensive and includes osteoarticular, dermatologic, gastrointestinal, and cardiovascular manifestations (Table 1) (9,52).

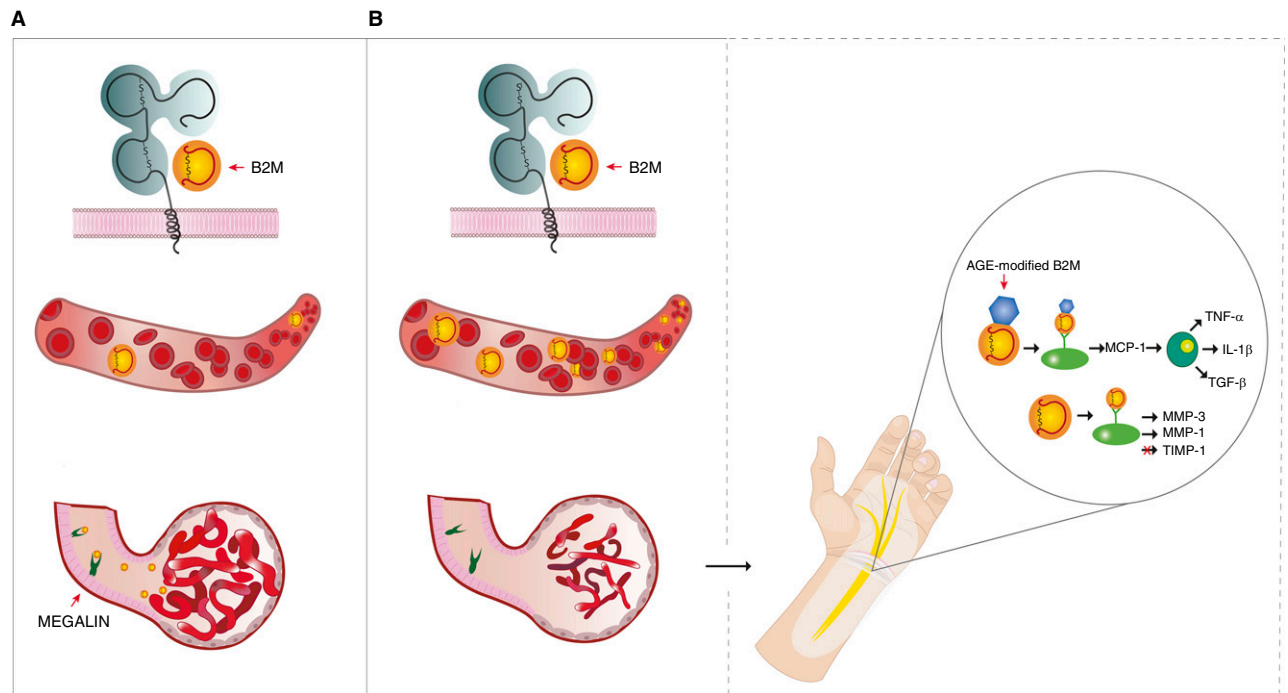


Figure 2. | $\beta 2$ Microglobulin (B2M) amyloidosis development involves advanced glycation end products (AGEs) with altered tissue metabolism. (A) Normally, plasma B2M molecules, shed from MHC 1 molecules, undergo glomerular filtration, bound by proximal tubular megalin receptors, and are endocytosed. (B) B2M accumulation in the circulation after reduction in glomerular filtration leads to (right panel) modification by AGEs with binding to fibroblast receptors for AGE in interstitial tissue. Monocyte chemotaxis and a cytokine-mediated inflammatory process involving TNF- α , IL-1 β , and TGF- β ensues. Unmodified B2M may produce cartilaginous destruction via altered expression of matrix metalloproteinase (MMP). MCP-1, monocyte chemoattractant peptide-1; TIMP-1, tissue inhibitor matrix metalloproteinase-1.

Typical symptoms of CTS include paresthesias, pain, and weakness associated with sustained hand or arm positions during sleep or repetitive motions. CTS manifestations are similar in patients on HD and those not on HD, but CTS in association with B2M-mediated DRA is more often bilateral and afflicts men and women equally (19).

Trigger-finger manifestations may range from localized tenderness to swelling and nodularity. In the most advanced stage of CTS, catching and locking are common. These signs occur most frequently after the onset of CTS (53).

Shoulder pain, due to amyloid deposition onto the coracoacromial ligament, is common and worsens during recumbent positions, such as during dialysis or at night, and is immediately relieved after moving to an upright or standing position. Tendinitis involving the rotator cuff and scapulo-humeral periarthrits may also appear.

B2M accumulation in the skin can lead to subcutaneous masses, lichenoid-plaque formations, and hyperpigmentation (52).

The above manifestations represent a significant effect on patient quality of life and can alert the clinician to the presence of amyloidosis. Fortunately, there is no effect on overall mortality.

Other severe phenomena that manifest at later stages of DRA can be life threatening: destructive spondyloarthropathy (DSA), fractures, gastrointestinal involvement, and cardiovascular amyloidosis.

First described in 1984 in patients on long-term HD, DSA more commonly affects the more-mobile cervical 5–7 and

lumbar 3–5 vertebrae (54). Amyloid has also been verified in lesions surrounding the spine, including the ligamentum flavum, zygapophysial (facet) joints, and intervertebral disks (55). DSA can produce difficulty in ambulation and loss of muscle mass. More dramatically, cervical cord compression with quadriplegia may result from extradural amyloid deposition (56). Lytic lesions of the bone can occur also in the hip and spine, leading to life-threatening pathologic fractures (57).

Importantly, DSA is not an “end stage” phenomenon. Some patients who have undergone treatment by intensification of HD and an apheresis column have demonstrated significant improvements in symptomatology and quality of life (58).

B2M amyloid deposition has occurred diffusely, including the submucosal vasculature and muscle layers of the tongue, stomach, small bowel, and rectum. These lesions have caused gastrointestinal system ischemia, perforation, and obstruction (59,60). B2M amyloid has also been insinuated in small- and medium-sized myocardial vessels, and cardiac valves (61,62). Although most cases of cardiac B2M deposition derive from autopsy specimens, vigilance for clinically relevant manifestations of heart failure and dialysis-induced hypotension must be ever present (63). Cases of cardiac amyloidosis attributable to B2M have declined, with the notable exception of Japan, where dialysis vintage often exceeds a decade (64).

Diagnostic Methods

A clinical diagnostic schema, made on the basis of major findings and minor findings, has recently been proposed in

Table 2. The pathophysiology of dialysis-related amyloidosis involves an inflammatory cascade and altered matrix metabolism

Mediator	Mechanism
Fibroblasts	Interactions with modified or unmodified B2M produce secretion of MCP-1 with monocyte attraction. MMP-3 leads to inflammation and tissue damage.
Monocytes	Attracted by MCP-1, monocytes differentiate into macrophages and contribute to inflammation <i>via</i> enhanced cytokine production.
MMP-1 and MMP-3	Proteinases, secreted by fibroblasts, produce cartilaginous injury by collagen and proteoglycan degradation.
AGE-modified B2M	Interaction with fibroblast RAGE results in endocytosis and transcription of genes involved in the inflammatory response.
Unmodified B2M	Interacts with fibroblasts resulting in MMP-1 secretion.
IL-1 β , TNF- α	Cytokines involved in the inflammatory response to B2M.
TGF- β	Cytokine found in amyloid deposits and has chemotactic activity for monocytes. Inhibits macrophage IL-1 β and TNF- α .

The principal participants are described. B2M, β -2 microglobulin; MCP-1, monocyte chemoattractant peptide-1; MMP-3, matrix metalloproteinase-3; AGE, advanced glycation end products; RAGE, receptor for AGE.

Japan (19). Major findings include multiple joint pains, CTS, trigger finger, dialysis-related spinal lesions, and bone cysts. Minor findings include bone fracture, ischemic colitis, or subcutaneous skin tumor. A definitive diagnosis is established by the presence of two major findings. Cases are labeled as doubtful if only one major finding plus one or

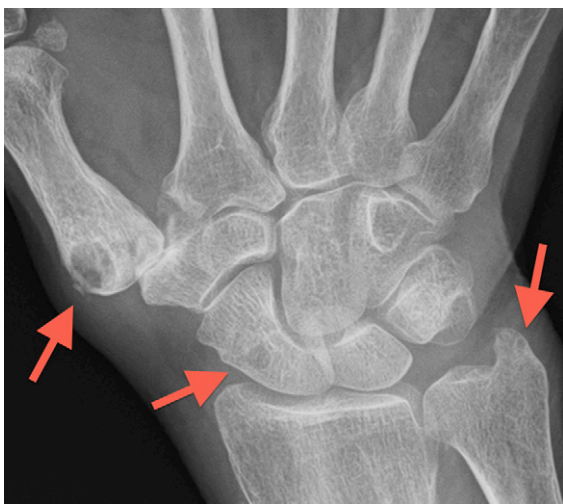


Figure 3. | Bone cysts in hand are characteristic of DRA. The presence of cysts in the hand and other bones (arrows) is an early complication of dialysis-related amyloidosis.

more minor findings are present. The severity of DRA symptoms can be classified as mild, moderate, or severe using a point system (65).

Imaging modalities that can detect DRA include plain radiography, ultrasonography, computed tomography, and magnetic resonance imaging. DRA is radiologically implied by radiolucent bone cysts, classically in hand and/or long bones (Figure 3). Magnetic resonance imaging is particularly helpful if thickened supraspinous or subscapularis tendons are detected. These lesions are also detectable by ultrasound (66,67). Radiologic findings of DSA are characteristic (Table 1).

Histology provides the gold standard for diagnosis; classic apple-green birefringence is demonstrated by Congo-Red staining. Typical biopsy sites are osteoarticular in origin. If other organs are involved, biopsy at these sites is feasible. However, abdominal fat pad biopsy is unwarranted in B2M amyloidosis (68). Amyloid deposits contain serum amyloid P (SAP), a glycoprotein that belongs to the pentraxin family and binds amyloid independently of the protein of origin. Consequently, radiolabeled SAP is a diagnostic imaging tool for amyloid (35), and SAP has been demonstrated in joints, carpal areas, and the spleen, among other organs (69,70).

Recently, an indium-111-labeled, recombinant B2M scintigraphic technique demonstrated equivalently sensitive identification of lesions labeled using iodine-131 native amyloid. This technique reduces exposure to exogenous plasma proteins and radioactivity (71).

Treatment

Treatment of DRA is divided into the care of established bone lesions and that directed at elimination of B2M, by resorption and/or enhanced elimination, and the prevention of future lesions.

Management of Established Lesions

Establishing a diagnosis of DRA validates a patient’s symptoms and is foundational for corrective treatments and palliative measures. The most debilitating aspects of DRA are pain, characteristically of the shoulders, hands, and back, and paresthesias. In addition to careful use of medical analgesia, the following surgical treatments have been proposed: surgical correction of CTS; arthroscopic or open shoulder surgery with removal of synovium infiltrated by amyloid, curettage, and bone grafting of amyloid cysts; and replacement of a diseased joint with a prosthesis, when required (72,73).

Treatment Directed at Amyloidosis

Some clinical subtypes of amyloid deposits can be resorbed and organ dysfunction reversed when amyloidogenic protein synthesis is decreased or clearance is increased. This principle is applied with liver transplantation in hereditary ApoAI amyloidosis (35). The same mechanism applies to DRA: reduce the serum concentrations below a critical threshold to prevent accumulation and ideally promote resorption.

Kidney Transplantation

Renal transplantation is the optimal method of reducing circulating B2M levels as treatment of amyloidosis (74). Symptoms improve rapidly after transplantation, especially shoulder pain and stiffness. This favorable outcome may, in part, result from concomitant glucocorticoid steroid administration. Iodine-131 labeling of native B2M scintigraphy revealed a reduction in the number of joints with radiotracer uptake. Nonetheless, no changes of established radiographic changes were observed, suggesting the reduction in radiotracer uptake is more related to decreased deposition rather than reabsorption (74).

Histologic documentation of amyloid deposition in osteoarticular surfaces for up to 20 years has been shown after kidney transplantation, concordant with the clinical observation of rapid symptom recurrence after allograft failure (75). A corollary of this observation is that multiple factors participating in improvement of symptoms after transplantation are at play, such as medications used, decreased inflammatory response, and cessation of new amyloid deposits.

Dialysis Techniques

High-flux membranes, increased HD duration, and hemodiafiltration increase B2M removal (Figure 4) (76–78). Nocturnal HD with 8-hour sessions for six nights per week, compared with thrice-weekly HD, nearly doubles B2M removal during a single session (26). The effect of high-flux versus low-flux HD has been described. Hemodiafiltration

(pre- or postfilter) leads to improved B2M clearance (79), and has been associated with decreased prevalence of CTS in a small case series (80). However, longer HD does not immediately translate to better results for all patients on dialysis, perhaps because of the heterogeneity of dialysis vintage and other patient characteristics (81,82).

Doxycycline and Metabolic Acidosis Treatment

In vitro, doxycycline inhibits amyloid fibrillogenesis. In one report of three patients with severe DRA, this tetracycline was associated with a reduction in pain and increased mobility (83).

Metabolic acidosis increases production of B2M, an effect that has been demonstrated *in vitro* and in healthy adults that were given ammonium chloride to induce metabolic acidosis (84). Therefore, on the basis of these observations, the maintenance of normal systemic pH is recommended.

B2M Adsorption

The Lixelle column (Kaneka Co., Osaka, Japan) was designed in the 1980s. This adsorbent column, placed upstream of the dialyzer in the extracorporeal circuit, has been therapeutically exploited since 1996 in Japan to enhance B2M clearance during HD (85,86). The column adsorbs B2M to cellulose beads with covalently linked hexadecyl groups *via* hydrophobic interactions (85). During a single HD session, the column increases plasma clearance of B2M from 51 ± 13 to 78 ± 8 ml/min ($P < 0.01$) (87). In a multicenter,

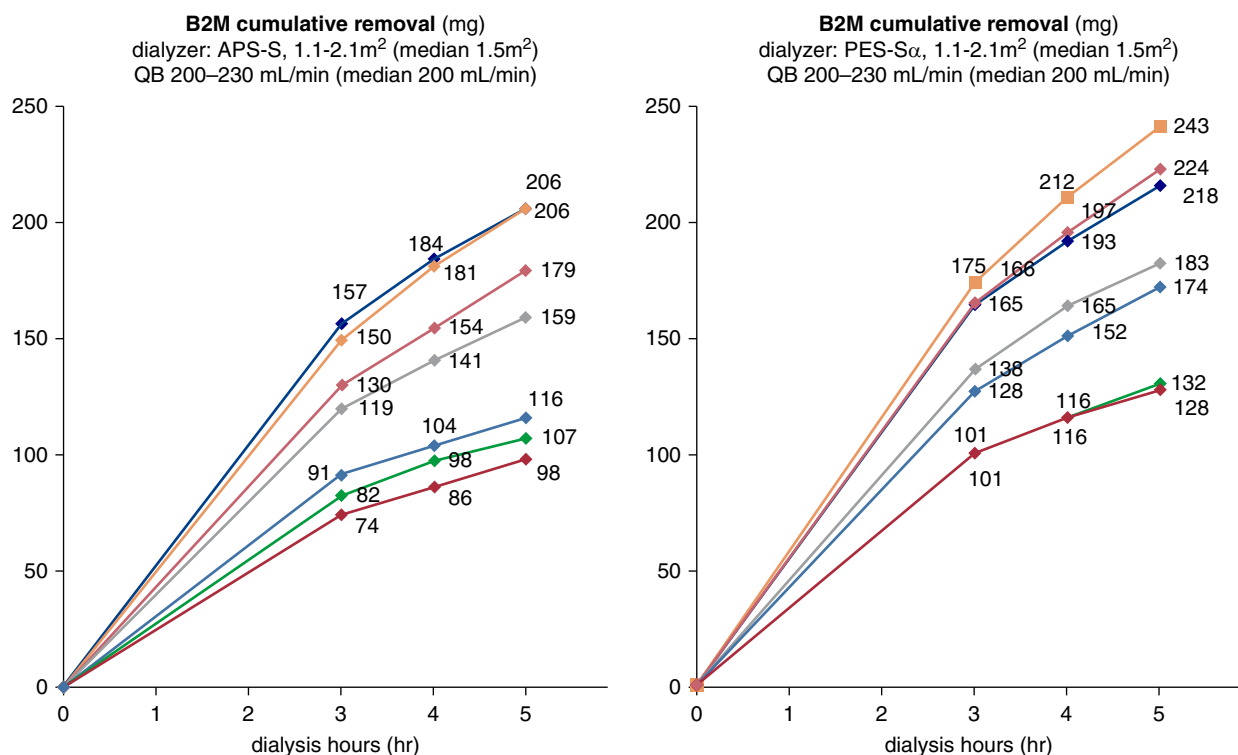


Figure 4. | B2M clearance during hemodialysis increases with treatment time. During a single hemodialysis session, spent dialysates from seven individual patients undergoing hemodialysis with an Asahi polysulfone (APS) or polyethersulfone (PES) membrane for times indicated. B2M removal increased during hemodialysis with variable reduction in removal rate after 3 hours of treatment. β 2m, B2M; QB, blood flow rate. Reprinted from results presented at the 54th Congress of the Japanese Society for Dialysis Therapy on June 7, 2009, with permission.

controlled study, the mean serum B2M concentrations of the treatment group were lower than the control group levels after the first and last treatments (7 ± 1 versus 11 ± 3 mg/L; $P < 0.01$) (87). Clinical scores of activities of daily living, pain, and stiffness improved significantly in subjects treated with the adsorbent column. The column also adsorbs proteins and other molecules with mol wts of between 4 and 20 kDa, including inflammatory cytokines, such as IL-1 β , IL-6, and IL-8, in addition to blood products (58). Therefore, reductions of not only B2M but also other molecular mediators are conceivably responsible for symptomatic improvements. Important limitations of these and other similar studies are worth considering. Neither the investigators nor study subjects were blinded. Two studies excluded patients with diabetes (87,88), and another (89) studied patients with a mean body mass index of 19.7 kg/m², thus the population differs from that commonly encountered in other countries. Adverse reactions associated with the Lixelle column include anemia and hypotension. In the study cited above, six of 22 subjects in the adsorption group discontinued treatment, two patients because of anemia and four because of hypotension (87).

Conclusions

An increasing number of persons worldwide continue to benefit from HD and its advances, yet DRA has come to be seen as a disappearing entity. However, because of the lack of regular, continuous B2M clearance, DRA remains a clinically important complication of intermittent HD. Patients with lesser burdens of comorbidity, who are not candidates for kidney transplantation, will likely live longer on RRT. For these patients, specific techniques of B2M removal, such as hemodiafiltration or an adsorbent column, may prove advantageous, but randomized controlled studies are needed (90). In the United States, the Executive Order of July 10, 2019 promoted increased utilization of hemodialysis methods (91). This Order may open and broaden the pathway for individualized dialytic treatments. Reducing β 2M accumulation-related clinical outcomes will require better identification of the high-risk population and evidence-supported decision making regarding treatment.

Disclosures

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Author Contributions

A. Fenves and I. Portales-Castillo wrote the original draft; A. Fenves, I. Portales-Castillo, and J. Yee conceptualized the study; I. Portales-Castillo was responsible for data curation, funding acquisition, investigation, methodology, project administration,

resources, software, supervision, validation, and visualization; I. Portales-Castillo and J. Yee were responsible for formal analysis; and all authors reviewed and edited the manuscript.

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