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 beta-2 microglobulin (B2M). Within that period, substantial advances in renal replacement therapy (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 end-stage kidney disease (ESKD) patients 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.
Introduction

More than 79 years after the first patient was successfully treated with hemodialysis, the prevalence of patients living with end-stage kidney disease (ESKD) continues to increase worldwide\(^1\). Unfortunately, not all individuals will be candidates for kidney transplantation, and those who remain on long-term hemodialysis (HD) may survive for decades. While 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 long-term HD patients was documented\(^3\). 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 abandoned after cases of bilateral CTS demonstrated independence from arteriovenous vascular access\(^5\).

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

Several years later, analysis of synovial amyloid revealed itself as beta-2 microglobulin (B2M), a 12,000 dalton molecule\(^7\). Similar deposits were discovered in biopsies of rectal mucosa from some of these patients, expanding the view of this disease as a systemic process produced by
B2M accumulation. B2M amyloid fibers involve almost every organ, except brain, leading to a variety of clinical entities described as “dialysis-related amyloidosis”.

Epidemiology and Risk Factors

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

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

The most dramatic demonstration of the decrease in DRA frequency is the study by Schwalbe et al. Here, the prevalence of DRA by clinical and radiologic parameters decreased by 80% from 1988 to 1996. CTS was diagnosed in 7 of 43 patients in 1988 but only 1 of 43 in 1996. Consequently, DRA was felt to be a disappearing entity. More recent data reveal that DRA remains an important complication of longer time on dialysis (Table 1 and Figure 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. More recently, a
population-based study from Taiwan that included 17,000 patients reflected a 10-year cumulative incidence of CTS in dialysis patients of 8.0% versus a 5.1% in matched, non-dialysis individuals\(^{20}\). Cases of CTS in the dialyzed group were more likely to receive surgical intervention than the control group (62.41% vs 12.89%), 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 patient requiring interventions for DRA complications has risen in some places\(^{22}\).

**Pathophysiology**

Before the discovery of B2M as amyloidogenic, proteolytic cleavage of native protein was considered essential to amyloid formation\(^{23}\). However, after the amyloid of dialysis patients was determined to have a similar molecular mass as intact B2M and X-ray crystallography demonstrated that almost half of amino acid residues of B2M participated in the characteristic beta-pleated sheets 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 beta chain of class I human leukocyte antigen (HLA-I) molecules and elimination are reviewed\(^{26}\). B2M is produced at a rate of 0.159 mg/hr per kg bodyweight (approximately 200–300 mg/day)\(^{27}\). B2M, shed into the circulation, undergoes glomerular filtration with subsequent near-total uptake by the proximal tubule receptor megalin and 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 generally are in the range of 25–35 mg/L. Inflammation, acidosis, and exposure to bioincompatible dialysis membranes among other influences, can increase B2M levels.

Hemodialytic clearance is a function of dialysis time and technique. Standard HD sessions provide but 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 grams, in contrast to 111 grams with a low-flux membrane. This one-third increase in B2M clearance plausibly explains why the dramatic reduction in DRA occurred after the late 1980s, i.e., use of high-flux membranes.

In vitro, investigations have demonstrated amyloid fiber formation from a concentrated sample obtained from carpal synovial tissue of HD patients, suggesting that elevated concentrations of B2M led to amyloid formation. Conversely, Zhang rendered a different conclusion regarding the role of high B2M levels in amyloidogenesis. In an animal model, employing B2M concentrations at 4-fold higher concentrations than in plasma from HD patients, spontaneous fibrillogenesis failed to occur, implying that elevated B2M concentrations alone were insufficient to produce amyloid. A separate observation in which a mutant thermodynamically unstable B2M variant produced amyloid at normal serum levels of B2M 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 prerequisite to amyloidogenesis, additional increases in plasma levels do not correlate with the risk of DRA.
The formation of amyloid fibers follows a classical nucleation-polymerization model in which a thermodynamically unfavorable nucleation reaction becomes favorable once a stable nucleus is formed\textsuperscript{33, 34}. High, local B2M concentrations at pH optimum of 2 to 3 units or stabilization of B2M molecules favors nucleation\textsuperscript{35}. Notably, this pH optimum is far lower than encountered in human physiology\textsuperscript{36}; however, polymerization of fibrils at physiologic pH might be supported by apolipoprotein E, proteoglycans, glycosaminoglycans, type 1 collagen, nonesterified fatty acid, and lysophospholipids\textsuperscript{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\textsuperscript{39}. Previously, HD was carried out with the copper-exposed Cuprophan\textsuperscript{®} dialyzer membranes that have been in disuse for more than three decades. As 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 composition of these now-defunct membranes\textsuperscript{40}.

Posttranslational modification and advanced glycation end-products (AGEs) likely participate in B2M amyloidogenesis\textsuperscript{41}. AGE-modified-B2M can interact with synovial fibroblasts that express AGE receptors (RAGEs)\textsuperscript{42, 43}, with consequent generation of monocyte chemoattractant peptide-1 (MCP-1) and monocyte chemotaxis to the locus of amyloid creation\textsuperscript{44} (Figure 2 and Table 2). B2M-exposed macrophages may then produce pro-inflammatory cytokines as well as regulatory cytokines such as the transforming growth factor-\(\beta\)\textsuperscript{45}. Conversely, unmodified-B2M interacts with collagen and fibroblasts, and increases secretion of matrix metalloproteinase-3 , which has broad capability for cartilaginous degradation\textsuperscript{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, 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.

**Clinical Manifestations**

The earliest evidence of DRA was documented from histologic samples, beginning about 2 years following initiation of HD. Symptoms due to amyloid deposition typically present after dialysis vintage of at least 5 years. With 30 years of HD, the majority of patients required surgical intervention for complications of DRA of which the clinical spectrum is extensive and includes osteoarticular, dermatologic, gastrointestinal, and cardiovascular manifestations (Table 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 HD and non-HD patients, but CTS in association with B2M-mediated DRA is more often bilateral and afflicts men and women equally.

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.
Shoulder pain due to amyloid deposition onto the coracoacromial ligament, is common and worsens during recumbent position such as during dialysis or at night, and immediately relieves after taking an upright or standing positions. Tendinitis involving the rotator cuff and scapulohumeral periarthritis 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 impact on patient quality of life and can alert the clinician to the presence of amyloidosis. Fortunately, there is no impact 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 long-term HD patients, DSA more commonly affects the more mobile C5–C7 and L3–L5 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\textsuperscript{59; 60}. B2M amyloid has also been insinuated into small and medium-sized myocardial vessels, as well as cardiac valves\textsuperscript{61; 62}. While 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\textsuperscript{63}. Cases of cardiac amyloidosis attributable to B2M have declined with the notable exception of Japan in which dialysis vintage often exceeds a decade\textsuperscript{64}.

**Diagnostic Methods**

A clinical diagnostic schema, based on major findings and minor findings, has been recently proposed in Japan\textsuperscript{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 more minor findings is present. The severity of DRA symptoms can be classified as mild, moderate, or severe using a point system\textsuperscript{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\textsuperscript{66, 67}. Radiologic findings of DSA are characteristic (Table 1).

Histology provides the gold standard for diagnosis; classical apple-green birefringence is demonstrated by Congo Red staining. Typical biopsy sites are osteo-articular in origin. If other organs are involved, biopsy at these sites is feasible. However, abdominal fat pad biopsy is unwarranted in B2M amyloidosis\textsuperscript{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\textsuperscript{35}, and SAP has been demonstrated in joints, carpal areas, and the spleen, among other organs\textsuperscript{69, 70}. Recently, an indium-111 labeled recombinant B2M scintigraphic technique demonstrated equivalently sensitive identification of lesions labeled using iodine-13a native amyloid. This technique reduces exposure to exogenous plasma proteins and radioactivity\textsuperscript{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 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\textsuperscript{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 increased. This principle is applied with liver transplantation in hereditary apolipoprotein A-I amyloidosis\textsuperscript{35}. The same mechanism applies to DRA, reduction of 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\textsuperscript{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 that the reduction in radio uptake is more related to decreased deposition rather than reabsorption\textsuperscript{74}.

Histological 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 following allograft failure. 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). Nocturnal hemodialysis with 8-hour sessions for 6 nights per week compared to thrice-weekly HD nearly doubles B2M removal during a single session. The effect of high-flux versus low-flux HD has been described. Hemodiafiltration (pre or post filter) leads to improved B2M clearance, and has been associated with decreased prevalence of CTS in a small case series. 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.

**Doxycycline and metabolic acidosis treatment**

In vitro, doxycycline inhibits amyloid fibrillogenesis. In one report of 3 patients with severe DRA, this tetracycline was associated with a reduction in pain and increased mobility.

Metabolic acidosis increases production of B2M, an effect that has been demonstrated in vitro and in healthy adults that were given NH4CL to induce metabolic acidosis. Therefore, based on 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\textsuperscript{85; 86}. The column adsorbs B2M to cellulose beads with covalently linked hexadecyl groups via hydrophobic interactions\textsuperscript{85}. During a single HD session, the column increases plasma clearance of B2M from 50.8±12.6 ml/min to 78.4±7.9 ml/min (P<0.01)\textsuperscript{58}. In a multicenter, controlled study, the mean serum B2M concentrations of the treatment group were lower than the control group levels after the first and last treatments (6.8±1.3 mg/L vs. 11.3±3.4 mg/L; P<0.01)\textsuperscript{87} Clinical scores of activities of daily living, pain, and stiffness improved significantly in adsorbent column-treated subjects. The column also adsorbs proteins and other molecules with molecular weights of between 4 and 20 kDa, including inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, in addition to blood products\textsuperscript{58}. Therefore, reductions of not only B2M but other molecular mediators are conceivably responsible for symptomatic improvements. Important limitations of these and other similar studies are worth considering. Neither the investigators or study subjects, were blinded. Two studies excluded patients with diabetes\textsuperscript{87; 88} and another \textsuperscript{89} studied patients with a mean BMI of 19.7, thus the population differs from the one commonly encountered in other countries. Adverse reactions associated with the Lixelle column include anemia and hypotension. In the study cited above, 6 of 22 adsorption-group subjects discontinued treatments, 2 for anemia and 4 for hypotension\textsuperscript{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 that are not candidates for kidney transplantation will likely live longer on renal replacement therapy. For these patients, specific techniques of B2M removal such as hemodiafiltration or an adsorbent column may prove advantageous, but randomized controlled studies are needed. In the United States, the Executive Order of July 10, 2019 promoted increased utilization of home dialysis methods. This Order may open and broaden the pathway for individualized dialytic treatments. Reducing β2M accumulation-related clinical outcomes will require better identification of the high-risk population and evidence-supported treatment decision-making.

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J Yee: Conceptualization; Formal analysis; Writing - review and editing

H Tanaka: Writing - review and editing
A Fenves: Conceptualization; Writing - original draft; Writing - review and editing

All authors contributed to the critical review, and generation of the final manuscript.
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Tables

Table 1

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>Prevalence after 10 Years of Hemodialysis</th>
<th>Clinical Manifestations</th>
<th>Diagnostic Clues</th>
</tr>
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<tbody>
<tr>
<td>Carpal tunnel syndrome (CTS)</td>
<td>10–20%</td>
<td>Hand pain, paresthesia, grip weakness</td>
<td>Bilateral manifestations in dialysis patients</td>
</tr>
<tr>
<td>Tendons</td>
<td>15%</td>
<td>Tendinitis: Shoulder pain, stiffness, trigger finger</td>
<td>Ultrasound or MRI findings of thickened supraspinous or subscapularis tendons, with lesser involvement of infraspinatus or teres minor tendons</td>
</tr>
<tr>
<td>Spine</td>
<td>20%</td>
<td>DSA: Back pain, neck pain, radicular pain, cord compression</td>
<td>Findings by conventional radiography or CT of narrowing of intervertebral spaces, severe bone erosions, cysts, and endplate destruction without significant amount of osteophyte formation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>&gt;30% of patients with evidence of DRA*</td>
<td>Pseudo-obstruction, bleeding, ischemia</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>Uncommon**</td>
<td>Heart failure, hypotension</td>
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Table 1. Clinical Manifestations of Dialysis Related Amyloidosis. Prevalence of dialysis-related amyloidosis increases with dialysis vintage. *Prevalence of gastrointestinal amyloidosis was derived mainly from histologic samples of patients exposed to older hemodialytic therapies who had no gastrointestinal complications. **Prevalence: Exact calculation of prevalence is not possible and depends on number of risk factors that increase with dialysis vintage. Symptomatic disease is uncommon before 10 years of dialysis vintage. Diagnosis: The gold standard is histopathologic demonstration of amyloidosis formation. CTS (carpal tunnel syndrome), DSA (destructive spondyloarthropathy), CT (computed tomography).

Table 2

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

Table 2. The pathophysiology of dialysis-related amyloidosis involves an inflammatory cascade and altered matrix metabolism. The principal participants are described. B2M (beta-2 microglobulin), MCP-1 (monocyte chemoattractant peptide-1); MMP (matrix metalloproteinase), AGE (advanced glycation end-products), RAGE (receptor for AGE), IL-1β (Interleukin-1β), TNF-α (tumor necrosis factor-α).
Figure Legends

Figure 1 | Development of hand bone cyst from b2-microglobulin amyloidosis increased between 2006 to 2013 in a Japanese hemodialysis facility. Cyst probability (red solid line; 1 – 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.

Figure 2 | β2-microglobulin (B2M) amyloidosis development involves advanced glycation end products (AGEs) with altered tissue metabolism. Normally, plasma B2M molecules, shed from major histocompatibility complex 1 molecules, undergo glomerular filtration, bound by proximal tubular megalin receptors, and endocytosed (panel A). B2M accumulation in the circulation following reduction in glomerular filtration (panel B) leads to modification by AGEs with binding to fibroblast receptors for AGE in interstitial tissue (panel C). Monocyte chemotaxis and a cytokine-mediated inflammatory process involving tumor necrosis factor-α, interleukin-1β, and transforming growth factor-β ensues. Unmodified-B2M may produce cartilaginous destruction via altered matrix metalloproteinase expression.

Figure 3 | Bone cysts in hand. The presence of cysts in the hand and other bones is an early complication of dialysis-related amyloidosis.

Figure 4 | Beta-2 microglobulin (B2M) clearance during hemodialysis from 7 patients. During a single hemodialysis session, spent dialysates from 7 individual patients undergoing hemodialysis with an (APS) or polyetheresulfone (PES) membrane for times indicated. B2M removal increased during hemodialysis with variable reduction in removal rate after 3 hours of treatment. Reproduced with permission. Results were presented at the "54th Congress of the Japanese Society for Dialysis Therapy" on June 7th, 2009.
Figure 1

Hand bone cyst free probability

<table>
<thead>
<tr>
<th>Strata</th>
<th>Number at risk</th>
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<td>All</td>
<td>150 117 101 79 60 49 37 25 17 2 1 1 1 1</td>
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<tr>
<th>Dialysis period (months)</th>
<th>0 24 48 72 96 120 144 168 192 216 240 264 288 312</th>
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<tr>
<td>Hand bone cyst free probability</td>
<td>0.00 0.25 0.50 0.75 1.00</td>
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Figure 2
**Figure 4**

**β2mg cumulative removal (mg)**
- **APS-S, 1.1-2.1m² (median 1.5m²)**
- **QB 200-230 mL/min (median 200 mL/min)**

**β2mg cumulative removal (mg)**
- **PES-S alpha, 1.1-2.1m² (median 1.5m²)**
- **QB 200-230 mL/min (median 200 mL/min)**