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1. Introduction

Amyloidosis is defined as an insoluble protein fibril that is deposited, mainly, in the extracellular spaces of organs and tissues as a result of a sequence of changes in protein folding. Precursor proteins change their conformation that forms amyloid fibrils, then deposited amyloid induce organ damage with disease specific conditions.

To date, there are 27 types of amyloidosis known extracellular fibril proteins in human, and each amyloidosis is characterized amyloid protein precursor, systemic (S) or localized organ (L), and syndrome or involved tissues [1]. In the nomenclature, dialysis-related amyloidosis (DRA) is defined as β\(_2\)-microglobulin-related (Aβ\(_2\)M) amyloid which precursor protein is β\(_2\)-microglobulin (β\(_2\)-m). It is associated to dialysis, a kidney replacement therapy, and deposits in systemic (S), mainly joint tissues [1].

Long-term dialysis treatment for end-stage kidney disease often induces the Aβ\(_2\)-m amyloid deposition in mainly osteoarticular tissues that induces various disorders, such as carpal tunnel syndrome (CTS), destructive spondyloarthropathy (DSA), and cystic bone lesions as well as in systemic organs such as heart and gastrointestinal tract when disease advances. Several biomolecules including β\(_2\)-m as well as clinical risk factors are thought to relate with Aβ\(_2\)M amyloidogenesis (Figure 1). Recent progress of dialysis therapy has improved survival of dialysis patients, however, older age and long-term dialysis treatment may increase the onset and acceleration of DRA. In this article, we described about DRA focused on pathogenesis, clinical manifestations and treatment, and showed DRA is still one of serious complications for patients undergoing long-term dialysis treatment.
2. Pathogenesis of dialysis-related amyloidosis

2.1. β₂-microglobulin

β₂-m is a polypeptide of 99 residues that has a molecular weight of 11.8 kDa. It forms the beta chain of the human leukocyte antigen (HLA) class I molecule and has a well-known β-sandwich structure that involves a 7-strand β-pleated structure stabilized with a single
disulphide bond (Cys25-Cys80). β2-m changes the conformation under various in vivo or in vitro conditions, such as acidic pH [2], 2,2,2-trifluoroethanol (TFE) [3], sodium dodecyl sulfate (SDS) [4], lysophospholipids [5], non-esterified fatty acids [6], heating [7] and agitation [8]. Proper dose of those molecules induce conformational intermediate that is required for Aβ2M amyloid fibril formation/extension (see below section).

2.2. Retention of conformational intermediate-β2-m

β2-m is a component of MHC class I molecules, which are present on all nucleated cells. Most β2-m is normally eliminated by the kidney via glomerular filtration and subsequent tubular catabolism with Megalin [9]. Thus, severe kidney damage induces the retention of β2-m in serum due to impaired excretion from the kidney.

Some clinical studies have attempted to identify the conformational intermediate form of circulating β2-m. Capillary electrophoresis reveals that patients undergoing hemodialysis due to end-stage kidney disease, but not healthy control subjects, have the conformational intermediate form of β2-m in serum [10]. The level of predialysis serum β2-m intermediate was 2.7±1.4 mg/L and native β2-m was 29.4±6.8 mg/L in 31 hemodialysis patients. Hemodialysis using a polymethylmethacrylate and online hemodiafiltration with a polysulfone membrane decreased the level of the native form, while any change in the intermediate form was variable [10]. These results suggest that intermediate β2-m is increased in hemodialysis patients and is difficult to remove with dialysis treatment. It may suggest that the intermediate form is immobilized in the extracellular space where Aβ2-m amyloid has a marked affinity for joint tissues (cartilage, capsule, and synovium). In addition, immunoaffinity–liquid chromatography–mass spectrometry analysis and immunoassay revealed the generation of lysine-58–cleaved and truncated β2-m (ΔK58-β2-m), which was found in serum from 20–40% HD patients but not in serum from control subjects [11]. However, this truncated form has not been demonstrated in the tissue containing Aβ2-m amyloid [12]. It is not certain whether the conformational intermediate or the truncated form of β2-m has a critical role of onset/progress of DRA, and future studies will be needed to understand the pathogenesis for Aβ2-m amyloid fibrils formation/extension.

2.3. Aβ2-m amyloid fibril formation and extension

A nucleation-dependent polymerization model explains the general mechanisms of amyloid fibril formation in vitro, in various types of amyloidosis [13-18]. This model consists of two phases, i.e., nucleation and extension phases. Nucleus formation requires a series of association steps of monomers, which are thermodynamically unfavorable, representing the rate-limiting step in amyloid fibril formation in vitro. Once the nucleus (n-mer) has been formed, further addition of monomers to the nucleus becomes thermodynamically favorable, resulting in rapid extension of amyloid fibrils according to a first-order kinetic model, i.e., via the consecutive association of precursor proteins onto the ends of existing fibrils [14, 17, 18].

In the mechanism of amyloidogenesis from β2-m, natively folded proteins, partial unfolding of protein is prerequisite to its assembly into amyloid fibrils [3, 13, 19, 20]. The extension of
Aβ2M amyloid fibrils, as well as the formation of the fibrils from β2-m are greatly dependent on the pH of the reaction mixture, with the optimum pH around 2.0-3.0 [13, 14]. At pH 2.5, where the extension of Aβ2M amyloid fibrils is optimum, β2-m loses much of the secondary and tertiary structures observed at pH 7.5 [13, 19]. Aβ2M amyloid fibrils readily depolymerize into monomeric β2-m at a neutral pH [19], however, low concentration of TFE [3] and sub-micellar concentration of SDS [4] induced Aβ2M amyloid fibrils extension with changing conformation of β2-m monomer and inhibiting depolymerization of amyloid fibrils at a neutral pH in vitro (Figure 2). While TFE and SDS are organic compounds, several biomolecules could induce Aβ2M amyloidogenesis in vivo, such as apolipoprotein E, proteoglycans, glycosaminoglycans, type1 collagen, non-esterified fatty acid, and lysophospholipids. [4-6, 21, 22]. For example, some lysophospholipids, especially lysophosphatidic acid (LPA) induces both

![Figure 2. β2-microglobulin-related (Aβ2M) amyloid fibril extension in vitro. Sub-micellar concentration of sodium dodecyl sulfate (SDS) induces Aβ2M amyloid fibrils extension at a neutral pH while micellar concentration induces amyloid fibril depolimerization in vitro. The amount of extended fibrils is measured by Thioflavin T (A), and observed by electron microscopy (B). Bar shows 250 nm.](image-url)
amyloid fibril formation and extension at a neutral pH [5]. The mechanism of amyloidogenesis is due to make β2-m monomer into partially unfolding the compact structure as well as stabilizing the extended fibrils in vitro. Clinically, plasma LPA concentration is higher in patients undergoing hemodialysis treatment as compare to healthy subjects [5]. It’s unclear the local concentration of lysophospholipids in the lesion that Aβ2M amyloid deposits, it may be reasonable to consider the reaction between β2-m and lysophospholipids that are increased in chronic kidney disease (CKD) undergoing dialysis treatment. Joint tissues that Aβ2M amyloid deposits at early stage in dialysis patients, contains many kinds of glycosaminoglycans and proteoglycans. Depolymerization of Aβ2M amyloid fibrils at a neutral pH in vitro was inhibited dose-dependently by the presence of some glycosaminoglycans (heparin, dermatan sulfate or heparin sulfate) or proteoglycans (biglycan, decorin or keratan sulfate proteoglycan) [21]. In addition, some glycosaminoglycans, especially heparin, enhanced the Aβ2M amyloid fibril extension induced by low concentration of TFE at a neutral pH [3]. These results suggest that some glycosaminoglycans and proteoglycans stabilize extended Aβ2M amyloid fibrils possibly by binding directly to the surface of the fibrils in vivo. Heparin is widely used for the hemodialysis treatment as an anticoagulant. Although no significant difference in the prevalence of Aβ2M amyloidosis was found between continuous ambulatory peritoneal dialysis patients and hemodialysis patients carefully matched for time on dialysis and age at the onset of dialysis [23], our study may suggest that heparin could exert a subtle effect for the development of Aβ2M amyloidosis under some clinical conditions.

Those molecules are picked up from the results of in vitro amyloid fibril formation, extension, and depolymerization, and further studies will be needed to analyze the histological relationship between those biomolecules and Aβ2M amyloid in the lesion.

2.4. Progress of bone disease after deposition of amyloid fibrils

It is not clearly understood the progress of bone disease after deposition of amyloid fibrils. Deposited amyloidosis induces compression that induced CTS and joint arthropathy. Also amyloid deposition induces local osteolysis that induced bone cysts and DSA. The progress through synovial inflammation and subsequent osteoclastogenesis and/or osteoclast activation through three possible pathways: (i) indirect action of inflammatory cytokines through the expression in osteoblasts of receptor activator of nuclear factor-κB ligand/osteoprotegerin ligand (RANKL/OPGL), (ii) direct action of inflammatory cytokines, and (iii) RANKL/OPGL expression in inflammatory cells.

3. Clinical manifestations

3.1. Serum β2-m levels in patients undergoing dialysis treatment

Advanced CKD induces the serum level of β2-m to elevate due to the impaired metabolism and excretion in the kidney. The average serum concentration levels of β2-m in patients undergoing dialysis is significantly higher compared to those in normal subjects (25–45 vs. 1–2 mg/L) [10, 24-27]. It is clearly understood that the impairment of metabolism in the kidney
is the main cause of fluid retention in HD patients; however, it is not clear whether the production of β₂-m is increased with CKD and/or dialysis treatment. However, a study shows that the amount of β₂-m on the surface of granulocytes, lymphocytes and monocytes in hemodialysis patients is higher than that in control subjects while mRNA expression of β₂-m in blood cells is no significant difference between them [28]. This result shows the possibility that increased binding of β₂-m to blood cells is one of major cause of retention of β₂-m in dialysis patients. Thus continuous higher serum levels of β₂-m could induced DRA after long-term dialysis treatment [24, 29].

3.2. Risk factors of DRA

Risk factors of DRA are (i) long-term dialysis treatment, (ii) initiation dialysis treatment in young age, (iii) hemodialysis treatment with low purity dialysate, (iv) use of low-flux dialysis membrane [30], while the pathogenesis of DRA with those risk factors is still incompletely understood. Recently it has trend to use high-flux dialysis membrane and high purity dialysate in hemodialysis treatment. However, progress of dialysis treatment as well as treatment for other diseases makes better survival of dialysis patients and older initiation of dialysis treatment. Thus long-term and old age dialysis patients increase, and DRA is still one of serious complications for patients undergoing dialysis treatment.

Serum level of β₂-m, precursor protein of DRA, increase in dialysis patients and is believed most important for onset and progress of DRA. While cross sectional study shows no relation between onset of DRA and serum level of β₂-m [24], DRA may be onset after accumulation of β₂-m with long duration of dialysis treatment [29].

3.3. Clinical manifestations

Long-term dialysis treatment for end-stage kidney disease often induces the Aβ₂-m amyloid deposition in mainly osteoarticular tissues that induces various disorders, such as CTS, DSA, and cystic bone lesions as well as in rarely systemic organs such as heart [31] and gastrointestinal tract [32] when disease is advanced. CTS is induced by the deposition of Aβ₂-m amyloid around synovium in carpal tunnel and the compression of median nerve. DSA is induced by the deposition of Aβ₂-m amyloid and the defect of bone in spine. It is radiographically characterized by severe narrowing of the intervertebral disk space and erosions as well as cysts of the adjacent vertebral plates. DSA lesions are mostly detected in the highly mobile areas, such as C5–C7 and L3–L5 [33]. Cystic lesions occur in bones, such as carpal and femur that Aβ₂-m amyloid deposition is found around them. Cystic lesions as well as mineral bone disorder associated with CKD increase the risk of bone fracture.

DRA, induce various osteo-articular disorders, is one of serious complications in patients undergoing long-term dialysis treatment even improvement of dialysis treatment such as dialysis membrane and dialysate [34, 35]. For example, we researched over a four year period 359 end-stage kidney disease patients undergoing dialysis treatment were admitted in our center for the treatment of their dialysis-related complications [34]. DSA was a major cause of hospital admission in the patients undergoing dialysis therapy for 20 years or more, and the
rate increased along with the increasing duration of dialysis therapy. The incidence rate of histories of surgeries for osteoarticular disorders, related to DRA was 25.0, 66.0, and 77.8 \% in 20-24 years, 25-29 years, and 30 years or more after the initiation of dialysis therapy, respectively (Figure 3). In the patients undergoing dialysis therapy for 30 years or more, the incidence rate of histories of surgeries for CTS, DSA, and joint arthropathy was 72.2\%, 50.0\%, and 22.2\%, respectively that indicated they had analogous histories of surgeries for various osteoarticular disorders (Figure 4). These results indicate that the frequency and severity of osteoarticular disorders which may be caused by DRA accelerated with the increasing duration of dialysis therapy especially for the patients undergoing dialysis therapy for 30 years or more.

Figure 3. The incidence rate of histories of surgeries for osteo-articular disorders, related to dialysis-related amyloidosis (DRA). The rate is 25.0, 66.0, and 77.8 \% in 20-24 years, 25-29 years, and 30 years or more after the initiation of dialysis therapy, respectively. In the patients undergoing dialysis therapy for 30 years or more, the rate for carpal tunnel syndrome (CTS), destructive spondyloarthropathy (DSA), and joint arthropathy was 72.2\%, 50.0\%, and 22.2\%, respectively.
Figure 4. A case of long-term dialysis patients complicated with various osteo-articular disorders related to dialysis-related amyloidosis (DRA). A man had end-stage kidney disease due to chronic glomerulo nephritis and received hemodialysis treatment for 30 years. He had various DRA-related osteo-articular disorders, such as carpal tunnel syndrome (CTS), joint arthropathy, and destructive spondyloarthropathy (DSA) that needed surgical treatment.

Next, we researched 102 patients undergoing dialysis treatment for 30 years or more in our related hospitals, and their complication of osteoarticular disorders. The age at initiation of dialysis therapy was $27.3 \pm 7.7$ years, and the duration of dialysis therapy was $32.3 \pm 1.8$ years. The surgery for CTS was done for 80 patients (76%) in $21.6 \pm 5.5$ years after the initiation of
dialysis therapy. All of those patients received the surgeries more than 2 times, furthermore, some of them received more than 4 times for 30 years or more. The surgery for DSA was done for 17 patients (16%) in 27.1 ± 4.7 years after initiation of dialysis treatment. There is dissociation in the incidence of history of surgery for DSA between in our center [34] and in our related hospitals while that for CTS was similar. The main reason may be that our center is a university teaching hospital and severe patients are referred to our hospital. This is a major limitation, however, it should be remembered that one of the main causes for admission was DSA in the patients undergoing long-term dialysis therapy. Our results may suggest that DRA is one of most serious complications in the patients undergoing dialysis therapy for 30 years or more. Further study will be needed about the detail of DRA in the in long-term dialysis patients. In our studies, the main factor associated with osteoarticular disorders which may be caused by DRA was the duration of dialysis therapy despite the younger age at initiation of dialysis therapy [34]. Other risk factors, such as dialyzer and dialysate could not be considered because of the consistent improvements in the technologies from year to year. For example, long-term dialysis patients had used the low-flux dialyzer for several years since initiating therapy, but now use a high-flux dialyzer. Short-term patients however, have used the high-flux dialyzer since the initiation of dialysis therapy.

In summary of our clinical research, the frequency and seriousness of osteoarticular disorders which may be caused by DRA were accelerated with the duration of dialysis therapy, especially in cases treated for 30 years or more.

4. Treatment for DRA

Main purpose of treatment for DRA is a) to prevent the deposition of Aβ2-m amyloid fibrils in the lesions, and b) to relieve symptoms induced by Aβ2-m amyloid deposition. Remove β2-m with dialysis treatment and suppression of systemic/local inflammation are beneficial to prevent the deposition of Aβ2-m amyloid fibrils. Practically, it should be used biocompatible high-flux dialysis membrane and high purity dialysate in hemodialysis treatment. In addition, hemofiltration, hemodiafiltration, and use of β2-m adsorption column have much effect to reduce β2-m and to improve symptoms [36]. Non-steroidal anti-inflammatory drugs or low dose of steroid sometimes show relief of symptoms induced by Aβ2-m amyloid deposition while use of steroid for long duration has risk to induce adverse effect, such as infection and osteoporosis. Surgical treatments are needed when Aβ2-m amyloid deposition induces severe osteoarticular symptoms.

4.1. Hemodialysis/hemodiafiltration

The use of high-flux dialyzer membrane leads to a reduction in the serum level of β2-m as compared to using low-flux dialyzer membrane. In the HEMO Study [26], the predialysis serum β2-m level was lower in the high-flux membrane group than in the low-flux membrane group. In another study, switching of dialyzer from conventional to high-flux membrane reduced the predialysis serum β2-m level [37]. Clinically, Küchle et al [38] examined the effect
of polysulfone high-flux dialysis membrane in hemodialysis treatment, and showed less onset of CTS, arthropathy and bone cysts as well as lower concentration of serum β₂-m as compare to use of low-flux dialysis membrane. The reason why high-flux membrane produces a lower level of serum β₂-m is not only that it promotes better clearance, but that it also increases the binding of β₂-m to blood cells, such as granulocytes, lymphocytes and monocytes [28]. High purity dialysate with low endotoxin reduced serum β₂-m, pentosidine, C-reactive protein, and interleukin-6 [39] that probably accelerates Aβ₂-m amyloid deposition.

Hemodiafiltration has better clearance of middle size molecules than HD and is known to reduce the risk of progression of DRA. A recent multicenter prospective randomized study revealed that on line HDF showed greater efficiency than HD with low-flux membrane in reducing the basal level of β₂-m [40].

4.2. HD with β₂-m adsorption column

A β₂-m adsorption column has been developed as a way to directly eliminate serum β₂-m. This adsorption column system is designed for direct hemoperfusion (Figure 5). Adsorption of β₂-m by this column is a result both of hydrophobic and molecular size-dependent interactions between the ligand in the column and β₂-m molecule. The effects of this column show the reduction rate; 60.0-78.9 %, the amount of adsorption; 157-300 mg, serum β₂-m after treatment; 6.8-13.5 mg/L with single treatment [41-43].

**Figure 5.** A schematic representation of hemodialysis treatment with β₂-microglobulin (β₂-m) adsorption column. The β₂-m adsorption column is placed in series with the dialyzer, with blood flowing through the column first.
According to a prospective multicenter study, a $\beta_2$-m adsorption column that was placed in series with a polysulfone dialyzer increased serum $\beta_2$-m reduction in patients undergoing hemodialysis as compared to hemodialysis treatment without $\beta_2$-m adsorption column [42]. This study also showed improvements of DRA-related symptoms, such as joint pain and activity of daily living, and it may suggest that the column absorbs not only $\beta_2$-m, but also other molecules related to inflammation. Furthermore, a clinical study showed shrink the size of bone cysts when they are checked by X-ray [43].

4.3. Other kidney replacement therapies

A significant inverse relationship is observed between residual renal function and serum $\beta_2$-m level [44]. This suggests that peritoneal dialysis may keep lower serum levels of $\beta_2$-m because of better maintenance of intrinsic renal function, but not peritoneal function, than hemodialysis. However the prevalence of histological DRA in peritoneal dialysis patients is not significantly different from that observed in a group of hemodialysis patients matched for age and dialysis duration [23]. End-stage kidney disease patients can do peritoneal dialysis only for 5-10 years, and it is difficult to discuss which treatment shows benefit to prevent DRA. A radical approach for DRA is kidney transplantation that reduces serum $\beta_2$-m, improves symptoms related to DRA and inhibits the progression [45]. The effects of kidney transplantation on DRA probably due to not only recover of kidney function but also effect of immunosuppression therapy.

4.4. Medical and surgical treatment

Use of steroid shows beneficial effect for the pain induced by DRA while surgical treatment will be needed for advanced CTS and DSA. However, DSA induces serious neurological symptoms and it is sometimes hard to relieve them with surgery. For example, 95 of 865 patients undergoing dialysis treatment had surgeries for DSA, while rate of post-operative complications, such as infection and cardiac events, was much higher than those without DSA [46].

5. DRA, a part of chronic kidney disease-mineral and bone disorder

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic disorder, which consists from abnormal levels of mineral-related biochemistries, bone abnormalities, and soft tissue calcification [47]. Various types of bone abnormalities are observed in CKD patients, such as high-turnover bone disease and osteomalacia. DRA causes bone abnormalities in patients undergoing dialysis treatment. Bone cyst, joint arthropathy, and DSA are frequency and specifically found in patients especially undergoing long-term hemodialysis therapy [48]. It remains controversial whether DRA and related osteopathy should be included in CKD-MBD. However, DRA is at least closely involved with CKD-MBD, from the view point of preventing osteoarticular complications in dialysis patients (Figure 6).
Figure 6. Dialysis-related amyloidosis (DRA) in chronic kidney disease-mineral bone disorder (CKD-MBD). CKD-MBD as well as DRA contains various types of bone abnormalities. Furthermore, β2-microglobulin/DRA may be involved with cardiovascular disease, bone fracture, and mortality which are clinical outcomes of CKD-MBD. In the view point of bone abnormalities, DRA may be related strongly with CKD-MBD.

CKD-MBD contains various types of bone abnormalities, such as high-turnover bone disease, osteomalacia, and adynamic bone disease. DRA, such as bone cyst, joint arthropathy and DSA, also causes bone abnormalities and is included in renal osteodystrophy. Recently, some groups reported the relation between serum levels of β2-m and atherosclerosis [49] or mortality [26], thus β2-m/DRA may be involved with cardiovascular disease, bone fracture, and mortality which are clinical outcomes of CKD-MBD. In the view point of bone abnormalities, DRA related osteopathy may enhance the serious bone disorder, such as bone fractures and DSA, in the presence of other bone abnormalities, such as high-turnover bone disease and osteomalacia. DRA is a serious complication in patients who are receiving long-term dialysis therapy and obviously seems more harmful than other osteodystrophy in terms of maintenance of their ADL and quality of life. Further studies will be needed for this assumption.

6. Conclusion

DRA is still one of major and serious complications in end-stage kidney disease patients undergoing long-term dialysis treatment. Several biomolecules that may relate to Aβ2-M amyloidogenesis are raised from in vitro studies, and that will be needed to investigate the
involvement in amyloid deposition in vivo. These findings will develop more beneficial prevention and treatment for DRA as well as improvement of dialysis treatment.

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