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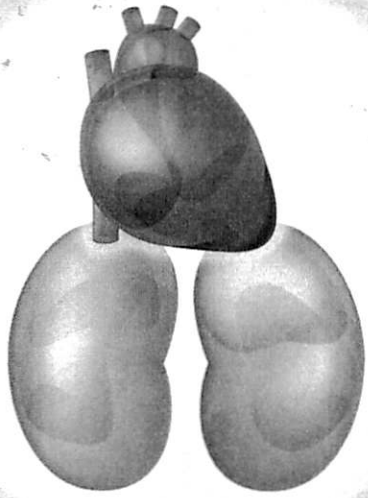

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UREMIC TOXINS

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16

β_2-MICROGLOBULIN

SUGURU YAMAMOTO, JUNICHIRO JAMES KAZAMA, HIROKI MARUYAMA, ICHIEI NARITA, AND FUMITAKE GEJYO

16.1 CHEMICAL STRUCTURE AND MOLECULAR WEIGHT

β_2-microglobulin 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 seven-strand β-pleated structure stabilized with a single disulphide bond (Cys25–Cys80) (Fig. 16.1a). β_2-microglobulin changes conformation under various *in vivo* or *in vitro* conditions. Far-UV spectra show that the fractions of β-sheet and β-turn decrease and the fractions of α-helix and random structure increase with several kinds of treatment, such as acidic pH,[1] 2,2,2-trifluoroethanol,[2]sodium dodecyl sulfate (SDS),[3] lysophospholipids,[4] nonesterified fatty acids,[5] heating,[6] and agitation.[7] A recent finding shows that the β_2-microglobulin mutant, K58P-W60G, where a Pro residue has been introduced in the type I β-turn, improves chemical and temperature stability and makes folding faster relative to native β_2-microglobulin.[8] These conformational changes and stability are pivotal for β_2-microglobulin-related amyloid fibril formation/extension (Fig. 16.1b), which induces dialysis-related amyloidosis (DRA).

16.2 METABOLISM AND BIOLOGY

β_2-microglobulin is a component of MHC class I molecules, which are present on all nucleated cells. Multiple myeloma, lymphatic leukemia, and malignant lymphoma,

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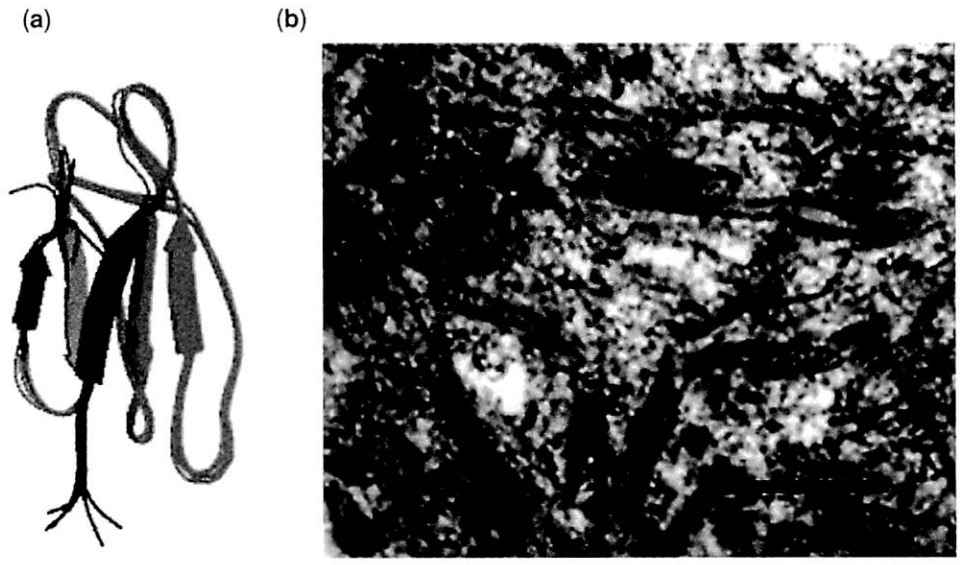


FIGURE 16.1 (a) Structure of β_2-microglobulin (PDB 1JNJ[34]). (b) Electron microscopy images of β_2-miroglobulin-related amyloid fibrils from carpal tunnel tissue in hemodialysis patients. Bar shows 1 μm.

as well as diseases with activation of the cellular immune system induce increased production of β_2-microglobulin in serum.

Most β_2-microglobulin is normally eliminated by the kidney via glomerular filtration and subsequent tubular catabolism. Megalin is a multiligand endocytic receptor involved in the endocytosis into lysosomes and metabolism of a wide variety of glomerular-filtered proteins, including β_2-microglobulin in the proximal tubule.[9] These proteins are metabolized in proximal tubular epithelial cells and the metabolites are recovered from general circulation via peritubular capillaries. Thus, proximal tubular injury increases β_2-microglobulin excretion in urine, while severe kidney damage induces the retention of β_2-microglobulin in serum due to impaired excretion from the kidney.

16.3 QUANTIFICATION METHODS

Serum level of β_2-microglobulin is usually measured using immunoassays, such as an indirect solid phase enzyme-linked immunosorbent assay (ELISA). β_2-microglobulin is the precursor protein for β_2-microglobulin-related amyloid fibrils and needs conformational change for *in vitro* fibril formation, as described above. Recent clinical studies have attempted to identify the conformational intermediate form of β_2-microglobulin. Capillary electrophoresis reveals that patients with chronic kidney disease (CKD) undergoing hemodialysis (HD), but not healthy control subjects, have the conformational intermediate form of β_2-microglobulin in serum.[10] The level of predialysis serum β_2-microglobulin intermediate was 2.7 ± 1.4 mg/L and native β_2-microglobulin was 29.4 ± 6.8 mg/L in 31 HD patients. HD using a

polymethylmethacrylate and online hemodiafiltration (HDF) with a polysulfone (PS) membrane decreased the level of the native form, while any change in the intermediate form was variable.[10] These results indicate that intermediate β_2-microglobulin is increased in HD patients and is difficult to remove with dialysis treatment. It may suggest that the intermediate form is immobilized in the extracellular space where β_2-microglobulin-related 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 β_2-microglobulin (ΔK58-β_2-microglobulin), 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 β_2-microglobulin-related amyloid.[12] It is not certain whether the conformational intermediate or the truncated form of β_2-microglobulin has a critical role of onset/progress of DRA, and future studies will be needed to understand the relationship.

16.4 PLASMA/SERUM LEVELS IN UREMIC PATIENTS AND HEALTHY SUBJECTS

Advanced CKD induces to elevate the serum level of β_2-microglobulin due to the impaired metabolism and excretion in the kidney. The average serum concentration levels of β_2-microglobulin in patients undergoing HD is significantly higher compared to those in normal subjects (25–45 mg/L vs. 1–2 mg/L).[10,13–16] 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 clearly understood whether the production of β_2-microglobulin is increased with CKD and/or dialysis treatment. β_2-microglobulin is the precursor protein of β_2-microglobulin-related amyloid fibrils in DRA, and continuous higher serum levels of β_2-microglobulin probably indicate the presence of carpal tunnel syndrome, one of the major symptoms induced by DRA.[13]

16.5 TOXICITY AND CLINICAL RELEVANCE

16.5.1 Adequacy of Dialysis Treatment

β_2-microglobulin, a middle-size protein, is a marker for adequacy of dialysis. A high serum β_2-microglobulin level and a low β_2-microglobulin Kt/V indicate that adequate dialysis for middle-size proteins has not been achieved. Generally, serum β_2-microglobulin is increased by reduced residual renal function, use of low-flux dialyzer membrane, and long-term dialysis treatment even with high-flux membrane.[15]

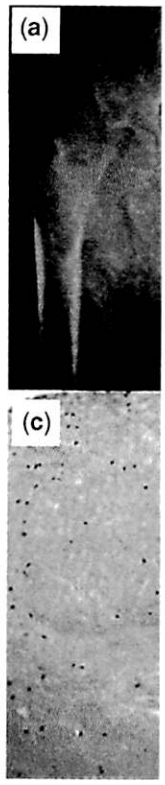
16.5.2 Mortality

In the randomized Hemodialysis (HEMO) Study, the relationship between serum β_2-microglobulin levels or dialyzer β_2-microglobulin clearance and mortality over

a period of 2.84 years was analyzed.[15] In time-dependent Cox regression models, predialysis serum β_2-microglobulin levels were associated with all-cause mortality after adjustment for residual kidney urea clearance and the number of prestudy years on dialysis.[15] In addition, Okuno et al. reported that higher serum β_2-microglobulin levels showed higher all-cause mortality and noncardiovascular mortality during 3.33 years.[16] In this study, there was no correlation between serum β_2-microglobulin and cardiovascular mortality. However, another cross-sectional study revealed that serum β_2-microglobulin is related with heart valve calcification, which is associated with carotid intima-media thickness in HD patients.[14] Furthermore, serum β_2-microglobulin levels were positively correlated with several cardiovascular risk factors, such as highly-sensitive *C*-reactive protein, troponin-T, myeloperoxidase, *N*-terminal pro-B-type natriuretic peptide and inversely correlated with prealbumin and ankle-brachial index.[17] These reports indicate that increased clearance for middle-size molecules, such as β_2-microglobulin, may induce less all-cause motality or less cardiovascular event/motality.

16.5.3 Dialysis-Related Amyloidosis

DRA is a form of general amyloidosis characterized by the deposition of β_2-microglobulin-related amyloid fibrils.[18] Long-term dialysis patients often have DRA-related clinical manifestations, such as carpal tunnel syndrome and destructive arthropathy associated with cystic bone lesions (Fig. 16.2). The tissue retention of β_2-microglobulin with dialysis treatment due to the persistence of high serum concentrations for long durations appears to be a prerequisite for the onset of DRA. In addition to the retention of β_2-microglobulin, partial unfolding of β_2-microglobulin is believed to be needed for its assembly into β_2-microglobulin-related amyloid fibrils, in combination with interaction of disease-related molecules, such as apolipoprotein E,[19] glycosaminoglycans,[2,20] proteoglycans,[20] and phospholipids.[4] Thus, accumulated β_2-microglobulin in dialysis patients forms amyloid fibrils with conformational change and stabilization of amyloid fibrils with several disease-related molecules. In addition to deposition of β_2-microglobulin-related amyloid fibrils, inflammation after infiltration of inflammatory cells induces various DRA-related manifestations. In the case of DRA-osteopathy, chronic inflammation is found in the lesion. Inflammatory cells often infiltrate into the synovial and/or disc tissue that contain β_2-microglobulin-related amyloid deposits,[21] and these inflammatory cells release inflammatory cytokines.[22] Thus, amyloid deposition induces local osteolysis 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 (Fig. 16.3).[23]



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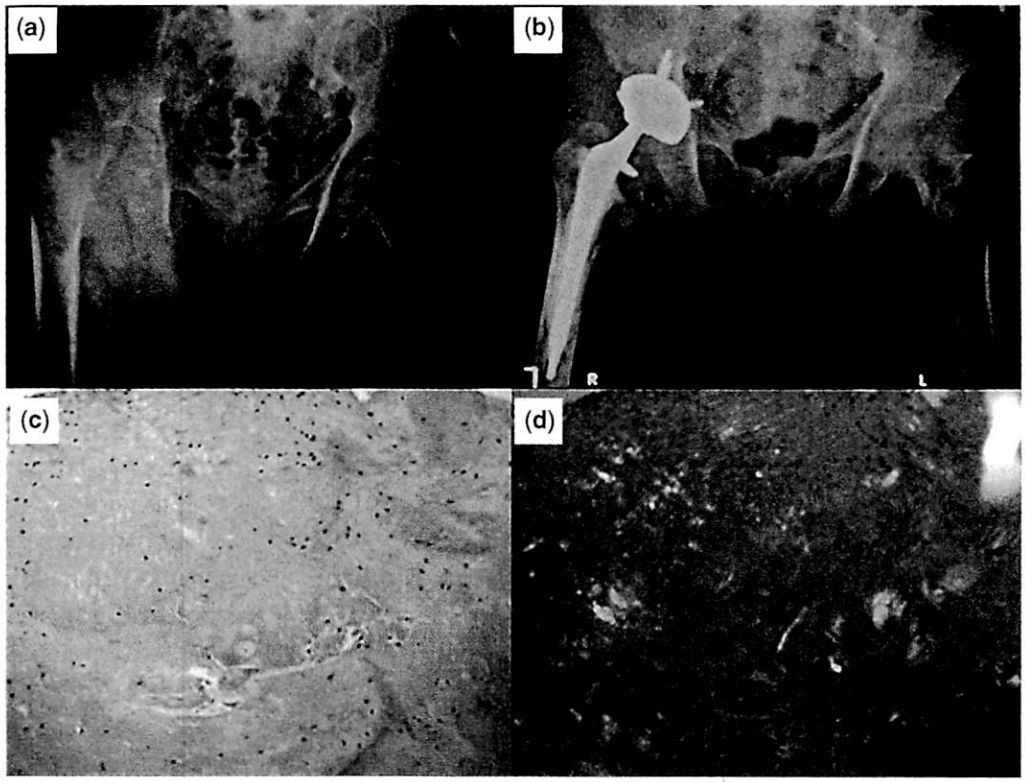

FIGURE 16.2 Destructive arthropathy in hip joint due to DRA. A 68 year-old man who had undergone hemodialysis for 34 years had rt. hip joint pain and gait disturbance. Bone X-ray showed destructive arthropathy of rt. femur neck (a), and the man underwent joint replacement (b). Congo-red (c) stained the tissue with orange-green birefringence under polarized light (d).

16.6 THERAPEUTIC METHODS TO REMOVE THE TOXINS

16.6.1 Dialysis Modality

Therapeutic options to improve serum β_2-microglobulin levels are to use several dialysis modalities, such as HD, HDF, and peritoneal dialysis. A significant inverse relationship is observed between residual renal function and serum β_2-microglobulin level.[24,25] This suggests that peritoneal dialysis may keep lower serum levels of β_2-microglobulin because of better maintenance of intrinsic renal function than HD, while the prevalence of histological DRA in peritoneal dialysis patients is not significantly different from that observed in a group of HD patients matched for age and dialysis duration.[26] A radical approach to reducing serum β_2-microglobulin is renal transplantation, which decreases it from 39 ± 6 to 3.8 ± 1 mg/L as well as improving DRA symptoms and inhibiting the progress of DRA.[27]

16.6.2 HD with High-Flux Membrane

The use of high-flux dialyzer membrane leads to a reduction in the serum level of β_2-microglobulin as compared to using low-flux dialyzer membrane. In the HEMO

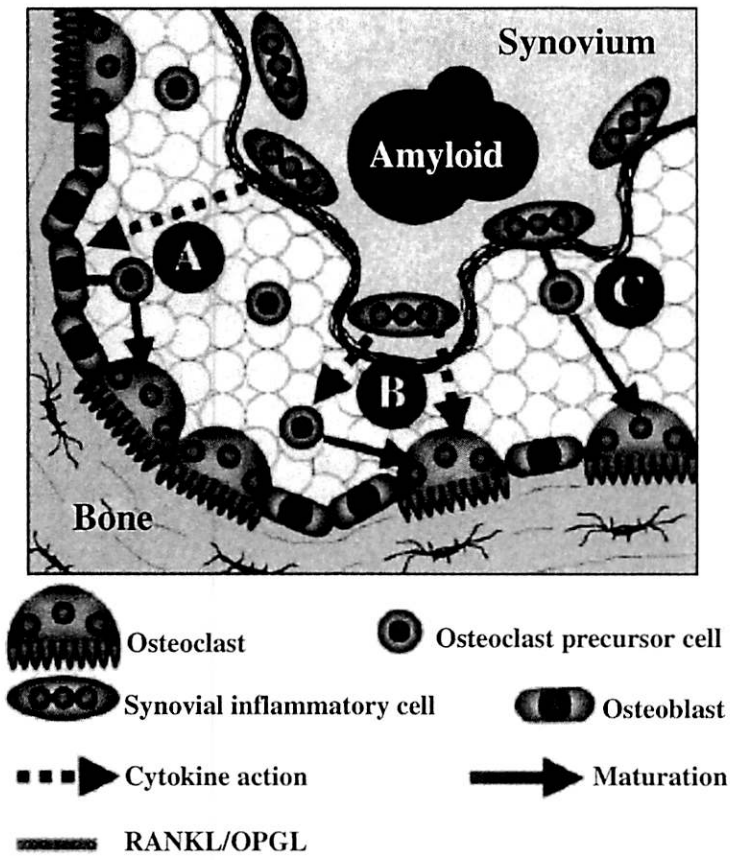

FIGURE 16.3 Possible pathways of bone resorption in DRA-osteopathy. (A) Inflammatory cytokines released from synovial infiltrating cells around amyloid deposits act on osteoblasts to express receptor activator of RANKL/OPGL on the cell surface. RANKL/OPGL promote osteoclastic bone resorption through direct contact to osteoclastic lineages. (B) Inflammatory cytokines released from synovial infiltrating cells around amyloid deposition act directly on osteoclastic lineages to promote bone resorption without the involvement of RANKL/OPGL. (C) Synovial infiltrating cells around amyloid deposits express RANKL/OPGL on the cell surface, and osteoclastic bone resorption is promoted through direct contact to osteoclastic lineages. Local administration of osteoprotegerin is expected to prevent osteoclastic bone resorption through pathways A and C.

Study, the predialysis serum β_2-microglobulin level was lower in the high-flux membrane group than in the low-flux membrane group (35.3 ± 11.2 mg/L vs. 41.7 ± 11.8 mg/L).[15] In addition, the rate of increase during 36 months was low in the high-flux membrane group.[15] In another study, switching of dialyzer from conventional to high-flux membrane reduced the predialysis serum β_2-microglobulin level by 22%, from 39.1 ± 11.2 to 30.5 ± 7.2 mg/L.[28] The reason why high-flux membrane produces a lower level of serum β_2-microglobulin is not only that it promotes better clearance, but that it also increases the binding of β_2-microglobulin to blood cells, such as granulocytes, lymphocytes, and monocytes. These cells have more β_2-microglobulin on the cell surface in the patients undergoing HD using high-

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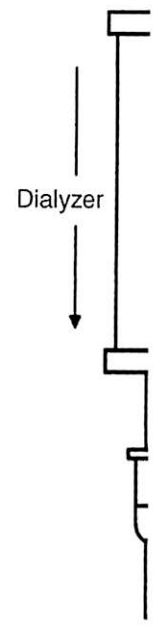

FIGURE 16.4
dialyzer and β_2

flux membrane compared to patients using low-flux membrane, while there is no significant difference in β_2-microglobulin mRNA expression in the cells among the groups.[29] Thus, high-flux membrane decreases serum β_2-microglobulin levels due to better clearance and less release from the surface of cells. These results indicate fewer onsets of DRA [28] as well as better survival[30] with HD using high-flux membrane compared to HD using low-flux membrane.

16.6.3 HD with β_2-Microglobulin Adsorption Column

A β_2-microglobulin adsorption column has been developed as a way to directly eliminate serum β_2-microglobulin, although limitations are encountered in removing β_2-microglobulin by the improvement of high-flux membrane alone. This adsorption column system is designed for direct hemoperfusion (Fig. 16.4). Adsorption of β_2-microglobulin by this column is a result both of hydrophobic and molecular size-dependent interactions between the ligand in the column and β_2-microglobulin molecule. At each standard HD treatment, the adsorption column is connected in series before arterial blood enters the dialyzer. According to a prospective multicenter study, a β_2-microglobulin adsorption column that was placed in series with a polysulfone dialyzer increased serum β_2-microglobulin reduction in patients undergoing HD as compared to the control group ($74.1 \pm 6.1\%$ vs. $60.1 \pm 6.3\%$).[31] This study also showed improvement of DRA-related symptoms, such as joint pain, and it

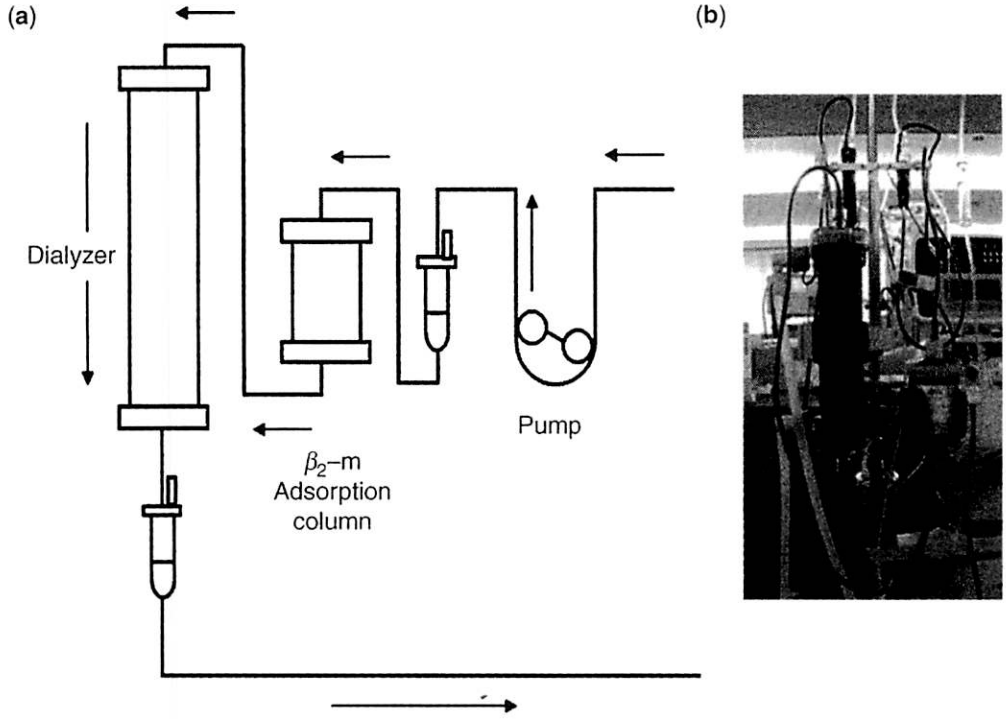

FIGURE 16.4 Schematic (a) and photographic (b) representation of blood flow through the dialyzer and β_2-microglobulin adsorption column.

may suggest that the column absorbs not only β_2-microglobulin, but also other molecules related to inflammation.

16.6.4 Hemodiafiltration

HDF has better clearance of middle-size molecules than HD and is known to reduce the risk of progression of DRA.[32] A recent multicenter prospective randomized study examined the treatments, A: HD with low flux for 6 months after high-efficiency online HDF for 6 months or B: high-efficiency online HDF for 6 months after HD with low flux for 6 months.[33] Online HDF showed greater efficiency than HD with low-flux membrane in reducing the basal level of β_2-microglobulin (22.2 ± 7.8 mg/L vs. 33.5 ± 11.8 mg/L) and of small sized molecules.[33]

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