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MINIREVIEWS

# Role of β2-microglobulin in uremic patients may be greater than originally suspected

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## Abstract

The role of beta2-microglobulin (β2M) in dialysis-related amyloidosis as a specific amyloid precursor was defined in the 1980s. Studies in those years were largely related to β2M amyloidosis. In 2005, for what was probably the first time in the available literature, we provided data about the association between β2M and early-onset atherosclerosis in hemodialysis patients without co-morbidities. In recent years, the role of uremic toxins in uremic atherosclerosis and the interest in β2M as a marker of cardiovascular (CV) and/or mortality risk have grown. In the current literature, clinical studies suggest that β2M is an independent, significant predictor of mortality, not only in dialysis patients, but also in predialysis patients and in the high-risk portion of the general population, and it seems to be a factor strongly linked to the presence and severity of CV disease. It is still unknown whether β2M is only a uremic toxin marker or if it also has an active role in vascular damage, but data support that it may reflect an increased burden of systemic atherosclerosis in a setting of underlying chronic kidney disease. Thus, although there have been some inconsistencies among the various analyses relating to β2M, it promises to be a novel risk marker of kidney function in the awareness and detection of high-risk patients. However, more research is required to establish the pathophysiological relationships between retained uremic toxins and further biochemical modifications in the uremic milieu to get answers to the questions of why and how. In this review, the recent literature about the changing role of β2M in uremic patients will be examined.

**Key words:** Beta2-microglobulin; Carotid atherosclerosis; Cardiovascular disease; Cardiovascular risk; Coronary artery disease; Hemodialysis; Mortality; Uremia; Uremic toxins



**Core tip:** Previously, the clinical significance of beta2-microglobulin (β2M) in uremic patients was limited to β2M-derived amyloidosis; in recent years, its role and power has changed and expanded. Although there have been some inconsistencies among the various analyses relating to β2M, the data generally support β2M as a promising novel marker of kidney function by predicting cardiovascular (CV) risk, CV events and overall mortality.

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## INTRODUCTION

Beta2-microglobulin ($\beta_2$M) forms the non-variable light chain of the Class 1 major histocompatibility complex (MHC). It is found on the surfaces of nearly all nucleated cells. It is a non-glycosylated polypeptide with a molecular weight of 11.729Da[1,2]. Due to its small size, $\beta_2$M is present in the glomerular filtrate of the normal kidney. It was originally discovered as a component present in the urine of patients with tubular proteinuria. It has been estimated that there are $10^5$-$10^6$ $\beta_2$M molecules/cell in human lymphocytes. When MHC is degraded, the MHC-associated $\beta_2$M is released into circulation[2-4]. This results in a constant production of free $\beta_2$M at a level of 0.13 mg/h × body weight in kilograms under normal conditions[2]. $\beta_2$M is found in low concentrations as a conformationally less restricted free monomer in blood and other biofluids, including synovial fluid. The normal physiological function, if any, of the freely circulating $\beta_2$M is unknown[2]. The $\beta_2$M synthesis rate in healthy individuals ranges from 2 mg/kg per day to 4 mg/kg per day, with a half-life of 2.5 h, and plasma concentrations vary between 1 mg/mL and 3 mg/mL[5].

Elevated $\beta_2$M levels are observed in chronic renal failures, lymphoproliferative disorders, inflammations, infections and other conditions as well, with high cell turnover[2]. A relationship has been noted between tumor burden and $\beta_2$M[6]. Concerning its use in oncology, $\beta_2$M levels correlate with the disease stage and poorer prognosis in patients with multiple myeloma and chronic lymphocytic leukemia[6,7]. It is also the most important predictor of treatment-free survival and overall survival of patients affected by lymphocytic leukemia and in most cases of lymphatic neoplasia. Additionally, serum $\beta_2$M levels can help to predict outcome in patients > or = 60 years with untreated acute myeloid leukemia[6,8]. Therefore, it is emphasized that $\beta_2$M may be the subject of future target therapy in cancer research[9].

Given that $\beta_2$M elimination is achieved *via* glomerular filtration, it is not surprising that plasma levels are inversely related to the glomerular filtration rate. Levels can be elevated as much as 60-fold in anuric patients with end-stage renal disease[5]. $\beta_2$M is a well-known, frequently studied representative marker of middle molecule uremic toxins and its role in dialysis-related amyloidosis as a specific amyloid precursor was defined in the 1980s[10]. Previous studies have largely been related to $\beta_2$M amyloidosis. However, its relationship with vascular risk was not identified until 2005. That year, to our knowledge for the first time in the available literature, we provided data on this relationship. We showed that, besides well-known cardiovascular (CV) risk factors, $\beta_2$M levels were independently related to carotid artery intima media thickness (C-IMT) in non-diabetic hemodialysis (HD) patients who had no clinical evidence of atherosclerosis[11]. Since then, the number of studies concerning this relationship has increased and now $\beta_2$M's direct pathophysiological role in vascular disease and its power as a predictor of overall and CV events are more predominant in the literature. In this review, the recent literature about the changing role of $\beta_2$M in uremic patients will be examined.

## $\beta_2$M-DERIVED AMYLOID

In long-term dialysis patients, retention of $\beta_2$M produces a disease related to the deposition of $\beta_2$M amyloid fibrils around large joints such as shoulders and hips. In 1980, Assenat *et al*[12] were the first to report finding amyloid in the material they had excised from their patients' carpal tunnels and in 1985, Gejyo *et al*[13] established a novel type of amyloidosis in patients undergoing HD. Initially, it was believed to occur only in patients on chronic HD; therefore, it was called "dialysis-associated amyloidosis". However, it soon became clear that amyloidosis could develop in patients on any type of renal replacement therapy and even in uremic and predialysis patients. Therefore, it came to be referred to as $\beta_2$M-derived amyloid or in line with general amyloid terminology, as A $\beta_2$M-amyloid[5].

### *Pathogenesis*

The exact mechanism of amyloidogenesis in dialysis patients remains unclear; however, elevation of circulating $\beta_2$M levels may not be the only cause of $\beta_2$M-derived amyloid. Recent studies have emphasized that in addition to substrate retention, biochemical modification of the $\beta_2$M molecule (such as oxidative modification) in the uremic milieu may potentiate its pathogenicity[14]. Glycosylated $\beta_2$M, a modified microglobulin, has been found in amyloid deposits as advanced glycation end products. This may further enhance the development of the lesions by both stimulating the secretion of cytokines and acting as chemoattractant and an apoptosis-delaying agent for monocytes. However, it remains unknown whether this modification plays an active role or is merely a long-term transformation of long-lived amyloid fibrils[14-17].

One of the other pathogenetic concepts in $\beta_2$M-derived amyloidosis is limited proteolysis and partial breakdown of native $\beta_2$M[5]. In recent years, a cleavage product form of $\beta_2$M that has a deletion of lysine at position 58 on the molecule $\Delta$K58-$\beta_2$M and behaves differently from normal $\beta_2$M has been demonstrated in the sera of 20%-40% of dialysis patients[18]. Although it is conformationally unstable and amyloidogenic *in vitro*, it was suggested that it could play a role in $\beta_2$M amyloid fibrillogenesis[19]. However, it was not detected by 2D electrophoresis in the *ex vivo* amyloid fibrils of

two patients affected by dialysis-related amyloidosis[20]. Based on this result, the authors concluded that the process of amyloid deposition "in a target tissue requires that the fibrillogenic protein attains the amyloidogenic conformation at the right site, at the right time, and at the right concentration". They further speculated that ΔK58-β2M might be more susceptible to degradation than to amyloid deposition. In contrast, a N-terminal truncated species lacking six residues, ΔN6-β2M which was highly amyloidogenic *in vitro* was not detectable in plasma[20]. The list of factors that have been shown to influence the conformation of intact β2M is very long. However, many of the *in vitro* conditions that are highly favorable for amyloid formation from normal β2M are not encountered *in vivo* because of the possibility that several factors may interplay in different ways *in vivo*[5].

### Clinical manifestations/diagnosis

This is a systemic type of amyloidosis but clinical manifestations of the disease are largely confined to the musculoskeletal system with carpal tunnel syndrome, spondyloarthropathies, hemarthrosis, joint pain and immobility. Late in the course of the disease, systemic deposition can occur, principally in the gastrointestinal tract and heart. Ninety percent of the patients may have the disease pathologically but not manifest clinical symptoms. Additionally, clinical symptoms are often nonspecific and easily mistaken for other articular disorders. The manifestations of β2M appear gradually over the course of years, between two and ten years after the start of dialysis in the majority of patients[2,5,21].

There are some suggestive findings, but no pathognomonic clinical or radiological findings exist in β2M amyloidosis. The gold standard diagnostic technique to demonstrate positive Congo Red staining and the presence of β2M is biopsy. Diagnostic material usually has to be obtained from synovial membranes or bone lesions[5,21].

### Treatment

There have been many studies addressing the effects of different dialysis membranes on serum β2M levels. Generally, it is recommended that non-cuprophane, high-flux dialyers should be used for patients with evidence of or at risk for β2M amyloidosis[21]. High-volume hemodiafiltration and ultrapure dialysate were also reported to be associated with increased β2M removal, lower serum concentrations and reduced inflammation[21-23]. However, dialysis of any kind or with any membrane is incapable of removing sufficient quantities of β2M to completely prevent the deposition of amyloid and, with the exception of kidney transplantation, no currently available therapy can stop the disease progression of β2M amyloidosis or provide symptomatic relief[21].

## β2M AND CARDIOVASCULAR RISK

In recent years, progressively more studies have been conducted with the aim of showing the involvement of uremic toxins and endothelial dysfunction in several aspects of uremic atherosclerosis[24]. Related to this, interest has grown in β2M as a marker of kidney function and CV risk.

### Pathogenesis

The role of serum β2M in the pathogenesis of CV disease is still not clearly known. However, there have been some suggestions. For example, β2M appears to damage vessels by participating in amyloid formation in the vascular wall[25]. Also, retained uremic solutes, such as β2M advanced glycosylated end products which have been substrates for oxidative injury, seem to further contribute to the proatherogenic milieu of uremia[14]. Additionally, it has been demonstrated that some uremic toxins inhibit endothelial proliferation and wound repair in uremic patients[26]. In the presence of uremic serum, endothelial progenitor cells, which contribute to vessel repair and neovascularization, undergo a decrease in their ability to migrate[27]. The influence of the uremic milieu was confirmed by the observation that high serum levels of β2M and indole-3-acetic acid were associated with low numbers of circulating CD34+CD133+ endothelial progenitor cells[28]. Another study investigated whether β2M was proinflammatory by inducing oxidative burst in leukocytes; β2M was not found to be a factor for induction of leukocyte free radical production[29]. However, the involvement of β2M in the inflammatory process and its association with vascular risk is still an area of interest deserving attention.

### Carotid atherosclerosis

In 2005, we investigated the associations of different risk factors with C-IMT, which had been an early marker of atherosclerosis, in "healthy" non-diabetic HD patients who had no clinical evidence of atherosclerosis[11]. In multivariate regression analysis, age, β2M, C-reactive protein and left ventricular hypertrophy were independently related to C-IMT. Elevated levels of β2M were found to be correlated not with the inflammatory markers but with the time patients had been in a uremic state. As we explained, although elevated plasma β2M was a well-known characteristic of chronic renal failure, that correlation may be just an epiphenomenon rather than a causal relationship, or β2M levels may indirectly influence uremia-related CV risk factors, or β2M *per se* may contribute to atherogenesis. As these were probably the first data about the importance of β2M as a CV risk factor in uremic patients, our findings necessitated confirmation in additional, larger scale studies. In 2006, using the same patient group, we assessed the determinants of the progression of C-IMT over the course of one year[30].

As in our former study, β2M was independently related to C-IMT at baseline; however, age and sex were the only independent predictors of the progression in C-IMT from baseline to the 12 mo stage. Subsequent studies in the general population showed that β2M was independently and significantly associated with total mortality and adverse CV outcome in patients with prevalent asymptomatic carotid atherosclerosis.

### *Peripheral arterial disease*

In 2007, Wilson *et al*[25] researched patients in the general population with and without peripheral arterial disease (PAD) and analyzed their plasma. The peak intensity of a 12 kDa protein was higher in patients with PAD. Western blot analyses and immunoaffinity studies confirmed that that protein was β2M and circulating β2M in PAD patients was elevated and correlated with the severity of the disease. Another study found no relationship between β2M and the augmentation index, either in patients with PAD or in healthy subjects. However, it did demonstrate that among patients with PAD, elevated plasma β2M levels were associated with higher aortic stiffness irrespective of CV disease risk factors[31]. Subsequent studies did not support this association between β2M and PAD[32]. Additionally, no changes were found in β2M levels in PAD patients after exercise on a treadmill, thus challenging the initial hypothesis by Wilson *et al*[25] of an increase in β2M levels in patients with PAD due to repeated bouts of ischemia-reperfusion[33]. Although the conflicting results mostly pointed to a non-specific elevation of β2M in patients with a high vascular risk, it was concluded that β2M levels may not indicate the presence of PAD, but may instead reflect an increased burden of systemic atherosclerosis in a setting of underlying chronic kidney disease (CKD)[31,32,34].

### *Coronary artery disease*

In 2007, we evaluated the determinants of coronary artery disease (CAD) other than conventional risk factors in nondiabetic HD patients[35]. Patients with CAD were compared to those without and, although β2M levels were higher in CAD patients (5.4 ± 1.4 mg/d *vs* 4.8 ± 1.5 mg/dL), the difference between the groups was not found to be statistically significant. The association between CV risk markers and arterial calcification in patients with CKD at Stages 3 and 4 had only recently been studied and β2M was found to be associated with coronary artery calcification beyond some other inflammatory biomarkers[36]. In addition, β2M, along with cystatin C and C-reactive protein, were found to predict mortality and improve risk classification and discrimination for a high-risk cohort undergoing coronary angiography[37].

### *Acute heart failure*

In a study evaluating the prognostic role of serum β2M in heart failure, patients with severe renal dysfunction were excluded and a higher baseline serum β2M concentration was found to be the most powerful predictor of cardiac events and cardiac mortality in acute heart failure patients with creatinine ≤ 3.0 mg/dL. Furthermore, the baseline serum β2M concentration had a superior ability to distinguish cardiac event risk in acute heart failure patients compared with creatinine-based renal parameters[38].

### *Left atrial size*

A linear correlation was found between the circulating levels of β2M and cystatin C and left atrial diameters. Additionally, left atrial diameters were negatively related to creatinine clearance in two study groups, one with CAD and the other without[39].

### *Arterial stiffness*

Arterial stiffness occurs due to loss of compliance of the vascular wall. It is a prominent feature of vascular ageing and strongly predicts CV and total mortality. β2M has been shown to be related to arterial stiffness in the general population[40]. In HD patients, β2M levels were found to be positively associated with pulse pressure, which is a result of arterial stiffness. Additionally, β2M levels were positively associated with insulin resistance[41].

## β2M AND ALL-CAUSE AND CARDIOVASCULAR MORTALITY

The HEMO study on 1704 HD patients showed that the predialysis serum β2M predicted mortality. After making statistical adjustments for the number of years on dialysis and for residual kidney function, for every 10 mg/L increase in the β2M level, there was a corresponding increase of 11% in mortality. The specific causes of death that account for this increased mortality have not been determined[42]. Another study evaluated the association of β2M levels in 490 HD patients with their clinical outcomes by dividing them into two groups according to their serum β2M levels[43]. Mortality from all causes in the higher β2M group was found to be significantly higher compared to that in the lower β2M group. These results demonstrated that serum β2M was a significant predictor of mortality in HD patients, independent of HD duration, diabetes, malnutrition and chronic inflammation[43].

The impact of β2M was studied in patients with CKD at different stages not yet on dialysis[44]. Baseline β2M levels were associated with vascular calcification but not with arterial stiffness. Higher β2M levels were independently associated with overall and CV mortality, with CV events in the whole cohort, and with CV events in the predialysis cohort. Furthermore, serum β2M was identified as an independent predictor of all-cause mortality in a population-based sample of older adults. Also, β2M was identified as a novel risk marker for adverse CV outcomes in patients with carotid

atherosclerosis[45].

### *β2M and infectious mortality in hemodialysis patients*

The HEMO Study Group examined the association of serum β2M levels and dialyzer β2M kinetics with cause-specific mortality. They focused on cardiac and infectious diseases which were the most common causes of death. There was no statistically significant association in that study between cumulative mean predialysis serum β2M levels and cardiac mortality. However, in the entire cohort, each 10 mg/L increase in serum β2M level was associated with a 21% increase in the rate of infectious mortality[46].

### *β2M and mortality and graft loss*

The association between post-transplant serum β2M and the outcomes following kidney transplantation were investigated. Serum β2M at discharge was a potent predictor of long-term mortality and of graft loss in kidney transplant recipients, providing information on the allograft function beyond that of serum creatinine[47].

## ENCAPSULATING PERITONEAL SCLEROSIS

This is a serious complication in peritoneal dialysis patients. β2M was found to be a useful screening test for the onset of encapsulating peritoneal sclerosis and β2M and the accumulation of middle-molecular uremic toxins were thought to be related to the pathophysiology of this disease[48]. Recently, the accumulation of advanced glycation end products and β2M in the fibrotic thickening of the peritoneum in long-term peritoneal dialysis patients was investigated. The proportion of β2M-expressing areas was found to be elevated in long-term peritoneal dialysis patients, which may be a marker of peritoneal injury[49].

## β2M AS A NOVEL MARKER OF KIDNEY FUNCTION AND RISK PREDICTION

Recently, there have been studies which evaluated whether novel biomarkers could add any information to improve risk prediction in patients at moderate and high risk. Data have provided that β2M, cystatin C and C-reactive protein predict mortality and improve risk classification and discrimination for a high-risk cohort. β2M and, to a lesser extent, beta trace protein, shared cystatin C's advantage over serum creatinine-based estimated GFR in predicting outcomes, including kidney failure. Thus, β2M shows promise as a novel filtration marker of kidney function for risk prediction of all-cause and CV mortality[50-52].

## CONCLUSION

Previously, the clinical significance of β2M in uremic patients was limited to β2M-derived amyloidosis; in recent years, its role and power have changed and expanded. Although there were some inconsistencies among the various analyses relating β2M to clinical outcomes, the data generally support β2M as a promising novel marker of kidney function by predicting CV risk, CV events and overall mortality. The exact role β2M plays in CV events and why it predicts CV and high risk of morbidity and mortality is still unclear. Further studies are needed to clarify the role of β2M in uremic patients.

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