β₂-Microglobulin: Its Significance and Clinical Usefulness

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ABSTRACT

β₂-Microglobulin (β₂M), an interesting and underutilized metabolite, can be used in assessing renal function, particularly in kidney-transplant recipients and in patients suspected of having renal tubulointerstitial disease. It also can serve as a nonspecific but relatively sensitive marker of various neoplastic, inflammatory, and infectious conditions. Early hopes that it would be a useful serum test for malignancy have not been fulfilled, but it does have prognostic value for patients with lymphoproliferative disease, particularly multiple myeloma. More recent reports have suggested a role for β₂M as a prognostic marker in human immunodeficiency virus (HIV) infection.

Introduction

Since its isolation in 1964 from the urine of patients with Wilson’s disease and workers exposed to cadmium, β₂-Microglobulin (β₂M) has elicited interest both as an indicator of renal function and as a relatively sensitive though nonspecific marker of certain malignancies, autoimmune diseases, and viral infections, most recently acquired immunodeficiency syndrome (AIDS). An overview is provided of the current status of β₂M assay with particular emphasis on its role in the management of lymphoproliferative disease and its prognostic value in HIV infection.

β₂-Microglobulin has been identified as the light chain common to the HLA-A, -B, and -C major histocompatibility complex antigens, and, as such, is expressed on the surface of virtually all normal nucleated cells as well as by many tumor cell lines. A low concentration of free β₂M, about 0.9 to 2.5 mg per L, is found in the serum of healthy subjects, apparently reflecting its “shedding” from the cell membrane as a consequence of the turnover of HLA. The surfaces of lymphocytes and monocytes are particularly rich in β₂M, and lymphocytic synthesis and expression are further augmented by stimulation with mitogens or with interferons. Although the function of surface β₂M remains...
obscure, increased concentrations of \( \beta_2 \)M in serum have been consistently observed in conditions characterized by lymphocyte activation and (or) proliferation. \( \beta_2 \)-Microglobulin may therefore serve as a useful nonspecific marker, in the absence of renal insufficiency, of systemic lymphocytic activation. In table I are described various immunological properties of \( \beta_2 \)M. In these settings, high serum \( \beta_2 \)M values can be thought of as a result of increased "synthesis" — whether owing to increased expression, increased HLA turnover, cell proliferation, cell lysis, or some combination of these — and not of decreased renal clearance.14

**Significance of \( \beta_2 \)M in Renal Disorders**

The unique features of the renal handling of \( \beta_2 \)M have prompted investigation into its role in evaluation of renal function, particularly in kidney transplant recipients and in patients suspected of having tubulointerstitial disease.24 By virtue of its low molecular mass (11800 Da), \( \beta_2 \)M is easily filtered through the glomerular basement membrane. Its rapid elimination is accomplished almost exclusively by glomerular filtration. Of the filtered \( \beta_2 \)M, 99.9 percent is then taken up by endocytosis into proximal tubular cells and catabolized into its constituent amino acids. Serum \( \beta_2 \)M determinations have been used to follow changes in glomerular filtration rate (GFR); urinary excretion above the normal maximum of approximately 370 \( \mu \)g per 24 hours is taken to indicate tubular dysfunction.

Both of these variables have been utilized in the management of renal-transplant patients, a setting in which rapid changes in GFR may be seen.13 In the presence of acute rejection, serum \( \beta_2 \)M concentrations typically become increased days before serum creatinine increases; furthermore, serum \( \beta_2 \)M values are independent of body mass or sex. A stable serum \( \beta_2 \)M in the face of postsurgical oliguria may help distinguish acute renal failure from rejection, and its increased urinary excretion may signify cyclosporin A toxicity.22 The use of \( \beta_2 \)M determinations must take into account their nonspecificity; however, because an increased serum \( \beta_2 \)M in this setting may be seen in systemic cytomegalovirus infection, it could prompt inappropriate high-dose steroid therapy if used as the sole criterion of rejection.3

\( \beta_2 \)-Microglobulin has also been determined in urine as an early indicator of aminoglycoside or lithium toxicity; to screen for heavy metal — (cadmium, mercury) — poisoning in appropriate populations; to help differentiate infections of the upper urinary tract from those of the lower urinary tract; and as an adjunct in the diagnosis of acute tubular necrosis.24

**Significance of \( \beta_2 \)M in Neoplasia**

An association between increased \( \beta_2 \)M in serum and the presence of malignancy was noted by several observers soon after the protein was characterized, prompting a flurry of reports concerning its possible use as a tumor marker (fig-
CLINICAL USEFULNESS OF $\beta_2$-MICROGLOBULIN

Figure 1. Concentration of serum $\beta_2$M in various B-cell neoplasias, solid malignancies, miscellaneous malignancies, and various benign infectious disorders. Gray stippled area on figure represents a number of subjects within the reference interval (0.9 to 3.0 mg per L) in the population studied.14

$\beta_2$-Microglobulin has since fallen prey to the difficulties encountered with other serum tests for cancer: disappearance of predictive power when applied to unselected populations, unacceptably low specificity, and the like.23 It has retained some favor as an adjunct in the staging of multiple myeloma (MM) and to a lesser degree in B-cell chronic lymphocytic leukemia (B-CLL), however, and may be of use in selected cases in other lymphoproliferative disorders.19

Bataille et al.4 correlated pre-treatment serum $\beta_2$M values for 115 MM patients with other prognostic features and with subsequent course. They found serum $\beta_2$M to have powerful predictive value independent of the effect of diminished creatinine clearance. Those patients with pre-treatment values $<$ six mg per L had a dramatically longer survival time (median, 52 months) than those with values $>=$ six mg per L (median, 26 months). Subsequent reports, with one exception,28 confirm the predictive power of serum $\beta_2$M assay and note significant correlation with stage and tumor cell mass.1 Carewail et al.16 found that, in some patients, serum $\beta_2$M appeared to correlate better with observed response to treatment than did changes in the concentration of the M-component. Serum $\beta_2$M values must be interpreted with caution in MM; however, although a statistically significant difference can be demonstrated between $\beta_2$M values in patients with "benign" monoclonal gammopathies and patients with stage I myeloma, there is a not inconsiderable overlap between the two
More importantly, there is a subset of patients with MM (eight of 90 in a 1987 prospective study) who never show an increase in serum $\beta_2$M.

The value of determining $\beta_2$M in patients with B-CLL is less well-established. Melillo et al showed a consistent increase in pre-treatment values for a group of 34 patients, as well as significant correlation with clinical stage (Stage I vs III or IV, Stage II vs III or IV; $P < 0.05$) and a significant ($P < 0.01$) decrease in values for patients responsive to therapy. However, the study confirmed earlier reports of a wide overlap between pre-treatment values and values in responders and also failed to show a return to normal concentrations in any patient. The latter likely reflects a “true” phenomenon, because complete eradication of the neoplastic clone in CLL is rare. Ellegaard et al concluded that repeated $\beta_2$M determinations in serum may be of value in estimating the residual tumor mass after therapy, a conclusion shared by other investigators.

Several studies have attempted to define a role for $\beta_2$M assay in the management of non-Hodgkin’s lymphoma (NHL) or in Hodgkin’s disease (HD). Although statistical correlations with stage at diagnosis and histological grade have been shown, the wide dispersion of values limits the usefulness of serum $\beta_2$M as a marker of disease activity. In addition, HD patients infrequently exhibit a significantly increased serum $\beta_2$M unless they have widespread disease. Measurements of $\beta_2$M in cerebrospinal fluid (CSF) may have value in detecting the presence of lymphoma or leukemia in the central nervous system, although repeat tests for recurrence must take into account nonspecific increases in CSF-$\beta_2$M owing to intrathecal chemotherapy.

Significantly increased values for serum are not limited to lymphoid malignancies and have been observed in some solid tumors as well (figure 1). The clinical utility of this observation is questionable, however. Lotzniker et al published a surprising result based on a study of 186 carcinoma patients. Those with stage IV disease had significantly lower serum $\beta_2$M values than those in stages II or III ($P < 0.01$). Immunohistochemical studies with use of antibodies to surface $\beta_2$M have shown a tendency for decreased expression in more poorly differentiated carcinomas. Lotzniker et al speculated that serum $\beta_2$M may serve as an interesting marker of differentiation rather than a tumor marker per se; decreased serum $\beta_2$M might directly reflect less tumor cell HLA turnover or may indicate an impaired immune response due to altered recognition sites.

Significance of Serum $\beta_2$M in Chronic Inflammatory Conditions and in AIDS

Serum $\beta_2$M values are increased in some chronic inflammatory or possibly autoimmune conditions, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, and Crohn’s disease, among others. Reviews of the utility of $\beta_2$M as a monitor of disease activity have been mixed. Dixon et al pointed out the difficulty of assessing the contribution of renal impairment to an increased value for $\beta_2$M in serum, particularly in patients who may have subclinical glomerular and tubular dysfunction resulting from chronic non-steroidal anti-inflammatory drug use. $\beta_2$-Microglobulin has been measured in synovial fluid and saliva in rheumatoid arthritis and Sjögren’s syndrome, respectively, and suggested as indices of lymphocyte turnover.

A $\beta_2$M response has been shown in certain viral infections, including infectious mononucleosis, cytomegalovirus,
non-A non-B hepatitis, and AIDS. The nonspecificity and variability of the response render it of little value for diagnostic purposes, although a high value in an immunosuppressed patient might prompt the clinician to consider the possibility of opportunistic viral infection. β₂-Microglobulin may also play a role in evaluating prognosis and monitoring treatment in HIV-infected patients. Bhalla et al reported above-normal concentrations in 29 of 31 AIDS patients as well as five of 11 asymptomatic homosexual men. Zolla-Pazner et al prospectively studied 40 asymptomatic homosexual men from New York City, whose cases were followed for two years. Six of the seven subjects with initial serum value >2.5 mg per L developed AIDS, whereas none of the remaining subjects progressed to AIDS during the two years. Recent reports at the Fourth and Fifth International Conference(s) on AIDS (Stockholm, June 1988 and Montreal, June 1989) continue to substantiate that serum β₂M is a useful surrogate test for predicting the development of AIDS. One paper, based on a prospective study of 215 HIV-antibody-positive subjects whose cases were followed for a median period of 30 months, suggested a multivariate model for predicting AIDS by use of serum β₂M determinations, CD4-positive lymphocyte counts, and measurements of anti-p24 and p24 antigen. In Table II is shown the relative risk of developing CDC Group IV disease. Another presentation suggested that a decrease or normalization of serum β₂M during the first eight to 12 weeks of azathioprine (AZT) therapy was predictive of a stable clinical status for 14 to 18 months. An additional report showed a strongly positive correlation between clinical severity of AIDS-dementia complex and β₂M concentrations in the cerebrospinal fluid.

Measurement of β₂M

There are several reliable methods quantifying β₂M, including laser nephelometry, radioimmunoassay, and enzyme immunoassay. The last two are the more sensitive and widely used techniques. These two methods allow detection of trace amounts of β₂M in normal serum and urine and effectively distinguish normal from high concentrations. β₂-Microglobulin is stable in serum, and samples can be stored at −20°C for as long as a year. Urinary assays are problematic, however, because β₂M is rapidly degraded at pHs <6.0. Although some investigators simply add alkali to the specimen, Schardijn recommends giving the subject four g of sodium bicarbonate on the evening before collection and an additional divided dose of four g during the 24 hour period to obviate degradation within the bladder.

**References**


