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Original article

Clinical utility of serum beta-2-microglobulin as a predictor of diabetic complications in patients with type 2 diabetes without renal impairment

M.K. Kim [a], K.-J. Yun [a], H.J. Chun [a], E.-H. Jang [a], K.-D. Han [b], Y.-M. Park [c], K.-H. Baek [a], K.-H. Song [a], B.-Y. Cha [a], C.S. Park [d,**], H.-S. Kwon [a,*]

[a] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 150-713, Republic of Korea*
[b] *Department of Biostatistics, The Catholic University of Korea, Seoul, Korea*
[c] *Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA*
[d] *Division of Cardiology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 150-713, Republic of Korea*

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Abstract

Aim. – As serum beta-2-microglobulin (B2M) levels are usually elevated in patients with renal failure, they have been suggested as a surrogate marker of cardiovascular mortality for patients with chronic kidney disease. Glycation of B2M is cytotoxic and may contribute to the risk of diabetic complications in patients with diabetes. Our objective was to evaluate the relationship between B2M and diabetic complications in patients with type 2 diabetes (T2D) and normal kidney function.

Methods. – A total of 366 patients with T2D and preserved renal function with no clinical evidence of cardiovascular disease were enrolled consecutively into this study. High B2M was defined as a median serum B2M level ≥ 1.8 mg/L. Subclinical atherosclerosis was defined as a carotid artery intima–media thickness (C-IMT) ≥ 0.9 mm or the presence of carotid plaque. The definition of diabetic nephropathy was based on the presence of albuminuria (≥ 30 mg/g creatinine).

Results. – Patients with high B2M were older, and had diabetes of longer duration, higher serum creatinine, microalbuminuria, and increased vascular stiffness and C-IMT compared with patients with low B2M. B2M levels were positively correlated with C-IMT and vascular stiffness, and these associations remained constant after adjusting for age. In addition, after adjusting for age, gender, body mass index, serum creatinine, hypertension, smoking and alcohol consumption, the adjusted odds ratio (OR) for atherosclerosis was 2.01 [95% confidence interval (CI): 1.02–3.94] per 1 mg/L increase in B2M. The prevalences of diabetic retinopathy and nephropathy were significantly higher with a high B2M than with a low B2M. The multiple adjusted OR for diabetic nephropathy was 2.29 (95% CI: 1.11–4.72) per 1 mg/L increase of B2M.

Conclusion. – Higher serum B2M was an independent risk factor for subclinical atherosclerosis and diabetic nephropathy in patients with T2D without renal impairment.

Keywords: Beta-2-microglobulin; Type 2 diabetes mellitus; Atherosclerosis; Complications

1. Introduction

Beta-2-microglobulin (B2M) is a small subunit of the major histocompatibility class I molecule, which is present on all nucleated cells [1]. Because it is non-covalently associated with the α chain and has no direct attachment to the cell membrane, free B2M circulates in blood after being shed from cell surfaces or by intracellular release. Once released, B2M is almost exclusively eliminated by glomerular filtration and has been used to determine the estimated glomerular filtration rate (eGFR).

* Corresponding author at: Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 150-713, Republic of Korea. Tel.: +82 2 3779 1039; fax: +82 2 786 1471.
** Corresponding author at: Division of Cardiology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 150-713, Republic of Korea. Tel.: +82 2 3779 1325; fax: +82 2 3779 1374.
E-mail addresses: Charlie@catholic.ac.kr (C.S. Park), drkwon@catholic.ac.kr (H.-S. Kwon).

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B2M concentration is fairly constant in healthy individuals [1], whereas blood levels of B2M increase in disease states such as renal dysfunction (due to reduced catabolism) and in certain malignancies, autoimmune diseases and infections (due to increased production). Serum B2M has been particularly useful as a clinical marker of chronic kidney-disease-related dysfunction [1].

The association between higher B2M concentrations and mortality is well known for patients on maintenance dialysis therapy [2]. Serum B2M levels are greatly elevated in patients on dialysis and contribute to amyloid deposition, with associated cardiovascular dysfunction. Thus, serum B2M has been suggested to be a surrogate marker of cardiovascular disease in patients with chronic kidney disease (CKD) [2]. Although B2M is a marker of renal function, its effect on all-cause mortality was independent of renal function in a prospective study of 1034 non-disabled people aged ≥ 65 years [3]. Thus, serum B2M levels are a novel predictor of all-cause and diabetes-related mortality in patients with diabetes regardless of renal function [4]. B2M is susceptible to advanced glycation end-product (AGE) modification and glycation; the latter renders it cytotoxic [5]. However, we are unaware of any study that has investigated whether serum B2M is associated with diabetic complications in patients with type 2 diabetes (T2D). Therefore, the present study examined the association between serum B2M and diabetic complications (subclinical atherosclerosis and diabetic microvascular complications), and included only subjects with preserved kidney function to clarify the role of B2M independently of kidney function.

2. Research design and methods

2.1. Study population

In the present cross-sectional study, 366 consecutive patients were recruited from October 2009 to January 2013, and referred to inpatient diabetes services for glycaemic control only. Inclusion criteria for this study were: age > 20 years; diagnosis of T2D; and normal kidney function [≥ 60 mL/min/1.73 m^2, as per the abbreviated modification of diet in renal disease (MDRD) formula]. Excluded were those with a history of type 1 or secondary diabetes, systemic infection, use of corticosteroids, pregnancy, or a history or evidence of myocardial, cerebrovascular or peripheral vascular disease. Patients with conditions known to be associated with acute-phase responses (those who had been hospitalized and/or treated during the previous two months for acute infection, malignancy, tuberculosis, chronic inflammatory disease or liver disease) were also excluded. The study was approved by the Institutional Review Board.

2.2. Measurements

Clinical information regarding the duration of diabetes, alcohol consumption (yes/no; heavy alcohol use was defined as five or more drinks per day in men, and four or more drinks per day in women), cigarette-smoking (yes/no) and other health-related variables were obtained using a standardized questionnaire. A venous blood sample was obtained in the morning after an overnight fast. HbA_{1c} levels were measured using an automated high-performance liquid chromatography analyzer (HLC-723 G7, Tosoh Corp., Tokyo, Japan). Levels of apolipoprotein A-1 (Apo-A1) and apolipoprotein B were determined by immunoturbidimetry, using a 7600 chemistry autoanalyzer (Hitachi Ltd, Tokyo, Japan). Serum B2M levels were measured by solid-phase, two-site, chemiluminescent immunometric assay (Siemens Healthcare, Erlangen, Germany). Arterial stiffness was assessed using brachial–ankle pulse wave velocity (PWV) (VP-1000; Omron Healthcare, Kyoto, Japan), while PWV was measured using a waveform analyzer (VP2000; Colin Medical Technology Corp., Komaki, Japan) after a 5-min rest in a supine position. The larger PWV value between the left (left upper arm to left ankle) and right (right upper arm to right ankle) was used for analysis. Subclinical atherosclerosis was determined using carotid ultrasonography. In accord with the Joint European Society of Hypertension/European Society of Cardiology guidelines [6], subclinical atherosclerosis in the carotid artery was defined as either an abnormally increased carotid intima–media thickness (C-IMT; ≥ 0.9 mm) or presence of carotid plaque. The presence of retinopathy was identified using ophthalmoscopy by a trained ophthalmologist after pupillary dilatation. Eye evaluation and photographic analyses of all study participants were performed by an experienced ophthalmologist who was blinded to the study. Based on this examination, retinopathy was classified as either absent or present. The urine albumin-to-creatinine ratio (U_{ACR}) was calculated from the first-voided spot urine sample. The definition of diabetic nephropathy was based on the presence of albuminuria (≥ 30 mg/g creatinine).

2.3. Statistical analysis

All data were analyzed using SAS version 9.1 software for Windows (SAS Institute, Cary, NC, USA). Data are presented as means ± standard deviations. A P value < 0.05 was considered significant. Pearson's correlation coefficients between B2M and various parameters were calculated. The median B2M level was 1.8 mg/L (range: 0.8–6.7 mg/L); a low B2M was defined as serum B2M < 1.8 mg/L and a high B2M was ≥ 1.8 mg/L. Student's t test and the χ^2 test were used to compare values between the high-B2M and low-B2M groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using binary logistic regression analysis to assess the associations between B2M and diabetic complications. A receiver operating characteristic (ROC) curve was designed to identify the cutoff values (thresholds) of B2M that best predicted diabetic complications. These cutoffs were derived by maximizing the sum of sensitivity plus specificity, with calculation of the 95% CI. Any additional prognostic value of B2M to other clinical predictors was assessed by the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [7]. Risk percentile cutoffs for NRI were approximately the 30th and 70th percentiles of predicted risk based on a multivariate model, the full inserted variables of which were age, gender, smoking, alcohol consumption, duration of diabetes, hypertension, HbA_{1c} level,