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Association Between Plasma Beta-2 Microglobulin Level and Cardiac Performance in Patients With Chronic Kidney Disease

Omid Sedighi [1]; Saeid Abediankenari [1,2,*]; Batoul Omranifar [3]

[1]Immunogenetic Research Center, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, IR Iran
[2]Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran
[3]Department of Cardiology, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, IR Iran

*Corresponding author: Saeid Abediankenari, Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran. Tel: +98-9121985667, Fax: +98-1513543087, E-mail: abedianlab@yahoo.co.uk

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Background: Beta-2 microglobulin (B2M) is considered as a surrogate marker for middle molecule uremic toxins and a key component in dialysis-related amyloidosis. However, few studies have evaluated role of B2M in patients with chronic kidney disease (CKD).
Objectives: The purpose of this study was to evaluate the association of plasma B2M level with some metabolic and cardiac performance factors in patients with CKD.
Patients and Methods: In this case-control study, we measured plasma B2M level in 86 patients with different stages of CKD and 78 age- and sex-matched individuals, as healthy control group. Then we investigated the association between plasma B2M level and left ventricular hypertrophy, ejection fraction (EF), and left ventricular end-diastolic diameter (LVEDD) in echocardiography and some inflammatory and metabolic factors in patients with CKD.
Results: Mean plasma B2M level was significantly higher in patients with CKD than in control group ($P < 0.001$). It was directly correlated with serum C-reactive protein ($r = 0.167$, $P < 0.001$), phosphate ($r = 0.112$, $P < 0.001$) levels, and left ventricular mass index ($r = 0.438$, $P < 0.001$) and LVEDD ($r = 0.275$, $P < 0.001$) in echocardiography. It was also inversely correlated with glomerular filtration rate ($r = -0.033$, $P < 0.001$), albumin ($r = -0.521$, $P < 0.001$), hemoglobin ($r = -0.748$, $P < 0.001$), and EF ($r = -0.625$, $P < 0.001$).
Conclusions: Our findings suggested that plasma B2M level is inversely associated with GFR and EF and directly correlated with some metabolic and cardiac performance factors.

Keywords: Chronic Kidney Disease; Cardiovascular Disease

1. Background

Beta-2 microglobulin (B2M) is a low-molecular-weight polypeptide (11800 Da), which is present on the surface of all nucleated cells, expressing the major histocompatibility class I (1). Under physiologic conditions, B2M is produced at a constant rate and is eliminated from circulation by kidneys. In patients with a range of inflammatory, hematologic, immunodeficiency, and renal diseases, plasma B2M levels are elevated (2).

In patients with chronic kidney disease (CKD), plasma B2M levels are elevated, especially in patients on hemodialysis (HD) in whom glomerular filtration rate (GFR) is almost completely absent (3). B2M is also a surrogate marker of middle-molecular-weight uremic toxins in patients on HD, which is cleared only by high-flux membrane (4). In some studies, predialysis serum B2M level predicted mortality and increase of B2M clearance during HD was associated with improved outcomes (5, 6). In addition, elevated plasma B2M level is a potential risk factor for the development of dialysis-related amyloidosis (7).

It is still unclear whether B2M is an important factor of cardiovascular mortality in patients with CKD (8). In some clinical studies, B2M had an active role in vascular damage by up regulation of interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) expression (9). In addition, it might cause cardiovascular disease by amyloid formation (10). However, in the other studies, higher serum B2M levels were associated with better nutritional status and survival in patients with CKD (11).

2. Objectives

The aim of this study was to determine the association of plasma B2M level with other serum inflammatory and nutritional markers and cardiac performance factors (systolic and diastolic function) in patients with CKD.

3. Patients and Methods

In this case-control study conducted in a nephrology clinic in Sari City, North of Iran, from February 2013 to April 2014, the participation of patients was voluntary and based on the invitation. Case group included 86 patients with different stages of CKD (estimated creatinine

clearances < 90 mL/min/1.73 m^2 [< 1.50 mL/s/m^2], calculated by Cockcroft and Gault formula, with duration of at least three months) and age of 30 to 70 years. Patients with stage V of CKD (estimated creatinine clearance < 15 mL/min/1.73 m^2 [< 0.25 mL/s/m^2]), presence of atrial fibrillation, complete heart block, and chronic inflammatory diseases, history of HD or kidney transplantation, and acute cardiovascular events in the preceding three months were excluded. This group of patients was compared with 78 age- and sex-matched healthy persons, as control group. The study protocol was approved by the local Ethics Committee and all patients signed an informed consent form.

3.1. Laboratory Tests

Fasting blood samples were collected from both case and control groups. After separation of serum from blood samples, the specimens were immediately transferred to the laboratory. Serum creatinine, blood urea nitrogen, total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, calcium, phosphorous, albumin, hemoglobin (Hb), C-reactive protein (CRP), and erythrocyte sedimentation rate were assayed by Pars Azmoon laboratory kits (Karaj, Iran), using an auto-analyzer (Prestige 24i, Japan). The plasma B2M concentration was measured by nephelometry method in basis of standard kit (Binding site, UK). Body mass index (BMI) was calculated by dividing body weight to square of height.

3.2. Echocardiography

Echocardiography measurements including two dimensionally guided M-mode echocardiograms (Vivid, USA, 2010) of the left ventricle were performed within two hours after blood sampling by a cardiologist unaware of the biochemical findings, according to recommendations of the American Society of Echocardiography (12). Left ventricular mass was calculated by Devereux and Reicheck formula (13) and indexed to body surface area to obtain left ventricular mass index (LVMI). Left ventricular hypertrophy (LVH) was defined as a LVMI > 115 g/m^2 in men > 94 g/m^2 in women (14).

3.3. Statistical Analysis

All date were analyzed by SPSS 17.0 (SPSS Inc. Chicago, IL, USA). Continuous variables were shown as the mean ± standard deviation. We compared qualitative and quantitative parameters between groups by Chi square test and independent-samples t test, respectively. We also used Pearson's correlation test to evaluate the association between variables. P values < 0.05 were considered as statistically significant.

4. Results

Table 1 illustrates the baseline clinical characteristics of patients with CKD (group I; n = 86) and healthy control subjects (group Π; n = 78). Mean age of patients with CKD and controls were 62.17 ± 16.52 and 58.61 ± 9.62 years, respectively. There were no significant differences regarding age, sex, and BMI between two groups. Mean plasma B2M level was significantly higher in patients with CKD than control group (P < 0.001). Table 2 shows echocardiography data of the study population. Table 3 shows the correlation between plasma B2M level and other clinical, biochemical, and echocardiographic profiles in patients with CKD.

Plasma B2M level was significantly and directly correlated with serum creatinine (r = 0.536, P < 0.001), CRP (r = 0.167, P < 0.001), and phosphate levels (r = 0.112, P < 0.001). It was also directly correlated with LVMI (r = 0.438, P < 0.001), interventricular septal thickness (r = 0.321, P = 0.002), left ventricular end diastolic diameter (LVEDD) (r = 0.275, P = 0.006), and left ventricular end systolic diameter (LVESD) (r = 0.155, P = 0.023). It was significantly and inversely correlated with GFR (r = -0.033, P < 0.001), albumin (r = -0.521, P < 0.001), Hb (r = -0.748, P < 0.001), and ejection fraction (r = -0.625, P < 0.001).

Table 1. Clinical and Biochemical Characteristics of the Study Population [a,b]

Parameter	Group I (n = 86)	Group II (n = 78)	P Value
Age, y	62.17 ± 16.52	58.61 ± 9.62	0.114
Gender			0.732
Male	46	41	
Female	40	37	
BMI, kg/m^2	22.14 ± 3.66	24.72 ± 6.18	0.641
Serum Cr, μmol/L	195.36 ± 68.95	76.02 ± 18.56	< 0.001
GFR, mL/min	48.2 ± 17.3	102.8 ± 31.6	< 0.001
Hemoglobin, g/L	112 ± 23.2	142 ± 35.2	0.002
Serum Calcium, mmol/L	2.29 ± 0.58	2.43 ± 1.10	0.173
Serum Phosphate, mmol/L	1.52 ± 0.39	1.39 ± 0.84	0.165
Albumin, g/L	31.8 ± 6.6	47.7 ± 12.3	0.012
C-Reactive Protein, nmol/dL	64.76 ± 43.81	29.52 ± 24.76	0.002
Total Cholesterol, mmol/L	5.99 ± 1.10	5.66 ± 1.86	0.621
LDL-Cholesterol, mmol/L	3.49 ± 0.84	3.14 ± 0.21	0.452
Triglycerides, mmol/L	2.68 ± 0.50	2.54 ± 0.35	0.663
Beta-2 Microglobulin, mg/L	7.6 ± 3.7	2.1 ± 1.7	< 0.001

[a] Data are presented as mean ± SD.
[b] Abbreviations: BMI, body mass index; Cr, creatinine; GFR, glomerular filtration rate; and LDL, low-density lipoprotein.

Table 2. Echocardiographic Data of the Study Population [a,b]

Parameter	Group I (n = 86)	Group II (n = 78)	P Value
Ejection Fraction, %	42.66 ± 8.23	57.92 ± 7.31	0.023
LVMI, g/m^2	118.73 ± 13.57	92.76 ± 8.34	< 0.001
Interventricular Septal Thickness, cm	1.58 ± 0.43	0.78 ± 0.38	0.007
LVEDD, cm	6.77 ± 0.85	4.53 ± 0.72	0.031
LVESD, cm	5.21 ± 0.52	3.21 ± 0.44	0.012

[a] Data are presented as mean ± SD.
[b] Abbreviations: LVMI, left ventricular mass index; LVEDD, left ventricular end-diastolic diameter; and LVESD, left ventricular end-systolic diameter.

Table 3. Correlation Between Plasma B2M Level and Selected Clinical, Biochemical, and Echocardiographic Data in Patients With CKD [a]

Parameter	Correlation (r)	P Value
Age, y	-0.081	0.431
BMI, kg/m^2	-0.116	0.225
Serum Cr, μmol/L	0.536	< 0.001
GFR, mL/min	-0.033	< 0.001
Albumin, g/L	-0.521	< 0.001
CRP, nmol/dL	0.167	< 0.001
Hemoglobin, g/L	-0.748	< 0.001
Calcium, mmol/L	-0.223	0.067
Phosphate, mmol/L	0.112	< 0.001
Total cholesterol, mmol/L	0.351	0.321
LDL-cholesterol, mmol/L	0.165	0.137
Triglycerides, mmol/L	0.215	0.209
Ejection fraction, %	-0.625	< 0.001
LVMI, g/m^2	0.438	< 0.001
Interventricular septal thickness, cm	0.321	0.002
LVEDD, cm	0.275	0.006
LVESD, cm	0.155	0.023

[a] Abbreviations: BMI, body mass index; Cr, creatinine; GFR, glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; LVEDD, left ventricular end-diastolic diameter; and LVESD, left ventricular end-systolic diameter.

5. Discussion

Our study showed that plasma B2M level was elevated in patients with CKD and this level progressively increased with decreasing GFR. Moreover, plasma B2M level was associated with some metabolic and cardiac performance factors in predialysis CKD patients. Kidneys eliminate B2M via glomerular filtration and tubular catabolism and hence, plasma level of B2M is highly correlated with GFR (3). Several studies have shown a significant correlation between plasma B2M level and some metabolic factors such as albumin in patients on HD (15). In addition, B2M is a main predictor of mortality in these patients, independent of other comorbidities such as diabetes, malnutrition, chronic inflammation, and HD duration (15). Liabeuf et al. reported plasma B2M level to be a predictor of overall and cardiovascular mortality and cardiovascular events in patients with different stages of CKD (16). Furthermore, Amighi et al. showed a strong association between serum B2M level and cardiovascular events in patients with prevalent asymptomatic carotid atherosclerosis, with comorbidity severity similar to patients with CKD, even after adjustment for CRP and GFR (17). Cheung et al. reported serum B2M level as a novel risk marker for all-cause and cardiovascular mortality in patients with diabetes mellitus, regardless of renal function (18). Shinkai et al. suggested that in old age population, the predictive value of plasma B2M level was superior to other established prognostic factors for mortality such as GFR, cystatin C, and CRP (19).

Wilson et al. identified that B2M is the most relevant biomarker in screening for peripheral artery disease, probably due to amyloid formation in the vascular wall (10). on the other hand, in another study, B2M was identified as a marker for nutritional status and its serum level was associated with better survival in patients on chronic HD (11).

The role of B2M in patients with CKD is unclear. Uremic milieu has a harmful effect on the cardiovascular system. In an in vitro study, high serum B2M and indole-3-acetic acid levels were with low CD34+ and CD133+ endothelial progenitor cells that contribute to vessel repair and neovascularization (20). Moreover, other uremic toxins such as P-cresyl sulfate and guanidine compounds might disturb endothelial proliferation and vascular repair mechanisms (21, 22).

Finally, our study had some limitations. First, we did not evaluate correlation between plasma B2M level and arterial stiffness while other studies have demonstrated this association in patients without CKD (23, 24). Second, this study had a single-center design with relatively small sample size and therefore, other multicenter studies with large number of participants are required to evaluate the role of B2M in cardiac performance in patients with CKD.

In conclusion, the results of our study showed that plasma B2M level was significantly and directly correlated with some cardiac performance factors such as LVMI, LVEDD, and LVESD. It was also significantly and inversely associated with GFR, albumin, Hb, and ejection fraction. Thus, B2M might have an important role in the development of cardiovascular diseases in patients with CKD.

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Authors' Contributions

Omid Sedighi: chief Manager; Saeid Abediankenari: laboratory tests consultant; and Batoul Omranifar: cardiology consultant and data collector.

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