Ischemia-Modified Albumin Is Associated with Arterial Stiffness in Hemodialysis Patients

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Summary

Increased arterial stiffness is strongly associated with cardiovascular morbidity and mortality in dialysis patients. Ischemia-modified albumin (IMA) is a useful biomarker of cardiac ischemia. This study was aimed to explore the association between IMA and arterial stiffness in hemodialysis patients. An observational study was conducted with 120 hemodialysis patients. Clinical data and laboratory characteristics were collected. Arterial stiffness was evaluated by brachial-ankle pulse wave velocity (baPWV). Hemodialysis patients had extensive arterial stiffness and high levels of IMA. Comparing to hemodialysis patients with normal baPWV, those with high baPWV had significantly higher levels of IMA (93.7 ± 8.6 versus 73.1 ± 10.7 Ku/L, \( P = 0.027 \)). The multiple linear regression analysis showed that IMA was significantly associated with arterial stiffness in hemodialysis patients (\( \beta = 0.43, \ P < 0.001 \)). Moreover, IMA, with a threshold value of 90.4 Ku/L, provided 77.4% sensitivity and 86.6% specificity for predicting arterial stiffness. Hemodialysis patients with arterial stiffness had high levels of IMA. IMA was a good predictive marker of arterial stiffness for hemodialysis patients.

Key words: Brachial-ankle pulse wave velocity, Risk factor, Cardiovascular disease, Inflammation

Cardiovascular and cerebrovascular diseases are the leading causes of death in hemodialysis patients, accounting for over 50% of deaths of known causes. Recently, increased arterial stiffness has been identified as a strong predictor for cardiovascular morbidity and mortality in dialysis patients. Pulse wave velocity (PWV) is a helpful and noninvasive technique to assess arterial stiffness. It has been demonstrated that PWV is an independent determinant of cardiovascular and all-cause mortality in hemodialysis patients.

Increased arterial stiffness in hemodialysis patients was found to be related to traditional cardiovascular risk factors such as age, hypertension, diabetes mellitus, and other atherosclerotic risk factors. However, other nontraditional risk factors such as advanced-glycation end products, endothelin, and shear stress are also associated with arterial stiffness. Ischemia-modified albumin (IMA) is a form of human serum albumin in which the N-terminal amino acids are unable to bind to transition metals. A great deal of studies demonstrated that IMA was a good biomarker for predicting major adverse cardiovascular events. In end-stage renal disease (ESRD) patients, Sharma et al. found that high IMA levels were correlated with a significantly larger left ventricular size, decreased left ventricular systolic function, and increased mortality. However, in hemodialysis patients, whether IMA is associated with arterial stiffness is not known. Recently, it was shown that high IMA is associated with vascular oxidative stress and inflammation. Thus, IMA may be a newly nontraditional marker of arterial stiffness.

In this study, we performed a prospective observational study to investigate the relationship between IMA and arterial stiffness in hemodialysis patients.

Methods

Study population: Between December 2016 and December 2017, 120 hemodialysis patients at the China-Japan Union Hospital of Jilin University were enrolled in this study. The hemodialysis patients received regular dialysis (three times a week and 4-5 hours per session) for at least 6 months. The exclusion criteria were the following: age < 18 years, suffering or having suffered once from acute infection, acute myocardial infarction, acute cerebral infarction, or severe hepatic or heart failure, and malignant tumor at the time of blood sampling. In addition, participants with serum albumin levels lower than 20 g/L or higher than 55 g/L were also excluded given that both malnutrition and overnutrition are nontraditional risk factors of arterial stiffness.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Jilin...
and right baPWV values was used for subsequent analysis.\(^{17}\) Then, baPWV was calculated from the formula
\[ \text{baPWV} = \Delta \text{height}. \]
Measurement of brachial-ankle PWV (baPWV):
Brachial-ankle pulse waveforms was determined. The length from brachium to ankles, and baPWV was assessed by a noninvasive vascular screening device (VP-1000; OMRON, Japan) using the method provided by the manufacturer. baPWV was measured in the morning on non-dialysis days. The time interval (\(\Delta T\)) between the wave fronts of the brachial and ankle waveforms was determined. The length from brachium to ankle (\(\Delta L\)) was calculated based on the participant’s height.\(^{17}\) Then, baPWV was calculated from the formula
\[ \text{baPWV} = \Delta L/\Delta T \text{ (cm/second)}. \]

Data were expressed as mean ± standard deviation or median [interquartile range]. baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; IMA, ischemia modified albumin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SOD, superoxide dismutase; and TC, total cholesterol.

University Ethics Committee. Written informed consent was also obtained from all the participants.

**Measurement of blood pressure and body mass index:**
For the hospitalized patients, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times using digital sphygmomanometers on non-dialysis days (OMRON Healthcare, Hoofddorp, The Netherlands) and the mean values of the three measurements were used as SBP and DBP in the analysis. Body mass index (BMI) was calculated by weight/height\(^2\) (kg/m\(^2\)). The body weight was calculated after dialysis.

**Biochemical measurement:**
All the venous blood samples were drawn at 6:00 AM after overnight fasting on a non-dialysis day. Laboratory parameters including glucose, creatinine, uric acid, albumin, total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) were measured by a standardized and certified program using an automatic biochemical analyzer (AU5800; Beckman Coulter, USA).

**Measurement of brachial-ankle PWV (baPWV):** To measure baPWV, cuffs were applied to both brachia and ankles, and baPWV was assessed by a noninvasive vascular screening device (VP-1000; OMRON, Japan) using the method provided by the manufacturer. baPWV was measured in the morning on non-dialysis days. The time interval (\(\Delta T\)) between the wave fronts of the brachial and ankle waveforms was determined. The length from brachium to ankle (\(\Delta L\)) was calculated based on the participant’s height.\(^{17}\) Then, baPWV was calculated from the formula
\[ \text{baPWV} = \Delta L/\Delta T \text{ (cm/second)}. \]

**Statistical analysis:**
Continuous data were expressed as mean ± standard deviation when in normal distribution, or median [interquartile range] in skewed distribution. Statistical analyses were done using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Differences of continuous variables between groups were determined by unpaired \(t\)-test, while categorical variables were compared using the Mann-Whitney \(U\) test. Multiple linear regression analysis was used to assess the independent factors associated with baPWV. Receiver-operating characteristics (ROC) curve analysis was used to quantify the predictive values of independent parameters for baPWV. A \(P\)-value < 0.05 (two-tailed) was considered to be significant.

**Results**

**Clinical and laboratory characteristics of the enrolled hemodialysis patients at baseline:**
A total of 120 hemodialysis patients (male/female: 64/56) were enrolled in this study. The mean age was 71.4(±7.6) years. Forty-six patients (38.3%) had diabetes and 74 (61.7%) had hypertension. The mean hemodialysis duration was 3.6 (1.2-12.4) years. The mean level of IMA was 85.5 Ku/L, while the mean baPWV value was 1457.7 cm/s. Other clinical and laboratory characteristics are shown in Table I.

**Clinical and laboratory characteristics of the two baPWV groups of hemodialysis patients:**
To explore the characteristics of the hemodialysis patients with high baPWV, we grouped the patients based on the values of baPWV; baPWV ≥ 1400 cm/s was considered to be high and indicated arterial stiffness. Figure 1 shows the baPWV values of the two groups. The high baPWV group had a significant higher baPWV value compared with that of the normal baPWV group (1723.5 ± 318.5 versus 1400 cm/s, \(P < 0.001\)). Compared with the normal baPWV patients, those with high baPWV had significantly higher levels of IMA (93.7 ± 8.6 versus 73.1 ± 10.7 Ku/L, \(P = 0.027\)), SBP (149.5 ± 24.8 versus 123.4 ± 11.3 mmHg, \(P < 0.001\)), DBP (84.1 ± 13.3 versus 78.4 ± 9.4 mmHg, \(P = 0.03\)), glucose (5.4 ± 1.9 versus 4.6 ± 0.8 mmol/L, \(P < 0.001\)), superoxide dismutase (SOD; 115 [98-134] versus 97 [80-114] U/mL, \(P = 0.0380\)), and high-sensitivity C-reactive protein (hsCRP; 4.35 ± 0.59 versus 3.41 ± 0.33 mg/L, \(P = 0.0450\)) (Table II).

**Correlation analysis for baPWV:**
To find the independent associated factors for baPWV, multiple linear regression analysis was used. As shown in Table III, IMA, hsCRP, and SOD were significantly associated with baPWV, and IMA had the strongest association with baPWV ≥ 1400 cm/second indicated arterial stiffness.\(^{18}\) In this study, we divided the patients into two groups according to the baPWV value as follows: the normal baPWV group was defined as having baPWV < 1400 cm/s, and the high baPWV group was defined as having baPWV ≥ 1400 cm/s.

**Measurement of IMA:** Serum IMA was measured by a colorimetric assay developed by Bar-Or, et al.\(^{19}\) This method is based on the principle of quantitative scanning of free cobalt present after cobalt binding has taken place. According to the manufacturer (Yi Kang, Co. Ltd., Changsha, China), the IMA upper limit is 85 kU/L.\(^{12}\)

**Table I. Clinical and Laboratory Characteristics of Enrolled Hemodialysis Patients**

| Hemodialysis (n =120) |  |
|----------------------|--------------------------|
| **Age (year)** | 71.4 ± 7.6 |
| **Sex ratio (male/female)** | 64/56 |
| **Duration of hemodialysis** | 3.6 (1.2-12.4) |
| **Hypertension (n, %)** | 74 (61.7%) |
| **Diabetes (n, %)** | 46 (38.3%) |
| **BMI (kg/m\(^2\))** | 21.5 ± 2.8 |
| **SBP (mmHg)** | 139.1 ± 24.2 |
| **DBP (mmHg)** | 81.8 ± 12.2 |
| **Glucose (mmol/L)** | 5.1 ± 1.6 |
| **Creatinine (umol/L)** | 1005.1 ± 305.1 |
| **Uric acid (umol/L)** | 419.7 ± 75.5 |
| **Albumin (g/L)** | 35.6 ± 4.7 |
| **TC (mmol/L)** | 4.7 ± 0.5 |
| **Triglycerides (mmol/L)** | 1.6 ± 1.2 |
| **LDL-C (mmol/L)** | 2.8 ± 1.0 |
| **SOD (U/mL)** | 102 (80-134) |
| **hsCRP (mg/L)** | 3.78 ± 0.41 |
| **IMA (kU/L)** | 85.5 ± 13.8 |
| **baPWV (cm/second)** | 1457.7 ± 326.2 |

Data were expressed as mean ± standard deviation or median [interquartile range]. baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; IMA, ischemia modified albumin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SOD, superoxide dismutase; and TC, total cholesterol.
baPWV (IMA, $\beta = 0.43$, $P < 0.001$; hsCRP, $\beta = 0.25$, $P = 0.032$; SOD, $\beta = 0.32$, $P = 0.016$). Other factors such as BMI, SBP, LDL-C, uric acid, glucose, albumin, and creatinine did not significantly contribute to high baPWV values (Table III). Moreover, we made a correlation analysis between IMA and baPWV. The result in Figure 2 implies that IMA was significantly associated with baPWV ($r = 0.69$, $P < 0.001$).

**Predictive value of IMA for baPWV in hemodialysis patients:** To analyze the predictive value of IMA for baPWV in hemodialysis patients, ROC analysis was performed. Figure 3 showed that the area under the curve (AUC) was 0.86 (95% confidence interval, 0.79-0.93, $P < 0.001$) for IMA. Furthermore, IMA, with a threshold value of 90.4 kU/L, provided 77.4% sensitivity and 86.6% specificity.

![Figure 1](image.png)

**Figure 1.** baPWV values of the baPWV groups. We grouped the patients according to the baPWV value as follows: normal baPWV group, baPWV < 1400 cm/second; high baPWV group, baPWV ≥ 1400 cm/second. baPWV indicates brachial-ankle pulse wave velocity.

**Table II.** Clinical and Laboratory Characteristics of Normal baPWV and High baPWV Hemodialysis Patients

|                        | Normal baPWV ($n = 48$) | High baPWV ($n = 72$) | $P$ value |
|------------------------|-------------------------|-----------------------|-----------|
| Age (year)             | 70.9 ± 7.9              | 71.6 ± 7.0            | 0.071     |
| Sex ratio (male/female)| 20/28                   | 40/32                 | 0.710     |
| BMI (kg/m²)            | 21.7 ± 3.1              | 21.2 ± 2.6            | 0.542     |
| DBP (mmHg)             | 123.4 ± 11.3            | 149.5 ± 24.8          | < 0.001   |
| DBP (mmHg)             | 78.4 ± 9.4              | 84.1 ± 13.3           | 0.030     |
| Duration of hemodialysis (years) | 3.7 (1.2-8.5) | 4.0 (2.1-12.4) | 0.543     |
| Hypertension (n, %)    | 35 (72.9)               | 39 (54.2)             | 0.322     |
| Diabetes (n, %)        | 22 (45.8)               | 24 (33.3)             | 0.623     |
| Glucose (mmol/L)       | 4.6 ± 0.8               | 5.4 ± 1.9             | < 0.001   |
| Creatinine (umol/L)    | 999.1 ± 299.9           | 1012.7 ± 316.6        | 0.650     |
| Uric acid (umol/L)     | 433.7 ± 79.8            | 410.7 ± 71.6          | 0.690     |
| Albumin (g/L)          | 36.9 ± 3.7              | 34.8 ± 5.1            | 0.0770    |
| TC (mmol/L)            | 4.7 ± 0.9               | 4.7 ± 1.1             | 0.140     |
| Triglycerides (mmol/L) | 1.4 ± 1.0               | 1.8 ± 1.2             | 0.110     |
| LDL-C (mmol/L)         | 2.9 ± 1.1               | 2.8 ± 1.0             | 0.950     |
| SOD (U/mL)             | 97 (80-114)             | 115 (98-134)          | 0.0380    |
| hsCRP (mg/L)           | 3.41 ± 0.33             | 4.35 ± 0.59           | 0.0450    |
| IMA (kU/L)             | 73.1 ± 10.7             | 93.7 ± 8.6            | 0.027     |

Data were expressed as means ± standard deviation. A $P$-value < 0.05 (two-tailed) was considered to be significant.

**Discussion**

In this study, we firstly investigated the relationship between IMA and arterial stiffness in hemodialysis patients. We found that IMA was a good predictive marker of arterial stiffness in hemodialysis patients.

Arterial stiffness is a common pathological change in hemodialysis patients and is involved in the high morbidity of cardiovascular events. Therefore, finding a simple and effective marker of arterial stiffness may help reducing cardiovascular morbidity in hemodialysis patients. Previous studies have shown that traditional cardiovascular risk factors play some roles in the progression of arterial stiffness before development of ESRD. But the enhanced rate of progression of arterial stiffness in hemodialysis patients was probably determined by more specific nontraditional ESRD-related risk factors such as advanced glycation end products. In our study, we found that IMA had a significant association with arterial stiffness evaluated through baPWV. This indicates that IMA may be a useful predictor of arterial stiffness in hemodialysis patients.

IMA was first discovered in the early 1990s and is a form of human serum albumin in which the N-terminal amino acids are unable to bind to transition metals. Albumin is the most abundant protein in human plasma, acting as a scavenger for divalent metal ions. The N-terminus of albumin binds metals, lipids, etc. In ischemia, the structure of albumin is altered due to the generation of free radicals and subsequent release of free iron and copper. Altered albumin (IMA) is unable to bind divalent metals and leave bound copper. In recent years, IMA has been found to be a useful and sensitive biomarker of cardiovascular disease in peritoneal dialysis patients and in patients after percutaneous coronary intervention. It was shown that continuous ambulatory peritoneal dialysis patients
with high levels of IMA (>85 kU/L) had lower non-MACE survival rates. In ESRD patients, Sharma et al. found that IMA levels were significantly associated with the bad changes of the cardiac structure and function. Moreover, IMA predicted mortality in patients with ESRD. High IMA levels have been documented in patients with acute coronary syndromes, heart failure, chronic liver disease, ESRD, diabetes mellitus, hyperlipidemia, and metabolic syndrome. These findings suggest that IMA formation may occur not only under acute but also chronic conditions such as chronic oxidative stress and inflammation. Increased IMA can in turn aggregate the severity of oxidative stress and inflammation. It is widely known that chronic inflammation and oxidative stress conditions exist in ESRD patients and that they are associated with arterial stiffness. In our study, we also found that patients with high baPWV had high IMA levels as well as high SOD and hsCPR levels. These results may indicate that the association between IMA and arterial stiffness reflected the chronic inflammation and oxidative stress conditions in the hemodialysis patients. In addition, during IMA generation, copper II was increased because it failed to be scavenged by human serum albumin. It has been demonstrated that copper II can induce inflammation, apoptosis, and oxidative stress, all of which are risk factors for arterial stiffness. Therefore, IMA may possibly promote arterial stiffness through elevated copper II. In fact, arterial stiffness induced vascular ischemia as well, especially for coronary artery. It was demonstrated that in ischemia, the generation of free radicals and acidosis development caused a change in the ability of the N-terminus of the protein to bind to transition metal ions and initiate IMA generation. It would be ideal to test whether lower IMA levels may improve arterial stiffness. However, there are still no reliable ways to modify the levels of IMA in clinical practice at present. Thus, whether there is a causal relationship between increased IMA and arterial stiffness needs to be further verified. Interestingly, although the hemodialysis patients with high baPWV had high SBP and glucose lev-

Table III. Multiple Linear Regression Analysis for baPWV

| Variable            | β        | P value |
|---------------------|----------|---------|
| BMI (kg/m²)         | 0.012    | 0.14    |
| SBP (mmHg)          | 0.15     | 0.12    |
| Glucose (mmol/L)    | -0.004   | 0.97    |
| Creatinine (μmol/L) | 0.14     | 0.13    |
| Uric acid (μmol/L)  | 0.039    | 0.66    |
| Albumin (g/L)       | 0.049    | 0.58    |
| LDL-C (mmol/L)      | 0.023    | 0.80    |
| SOD (U/mL)          | 0.32     | 0.016   |
| hsCRP (mg/L)        | 0.25     | 0.032   |
| IMA (kU/L)          | 0.43     | <0.001  |

β for multiple linear regression. A P-value < 0.05 was considered to be significant. baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; IMA, ischemia-modified albumin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and SOD, superoxide dismutase.

Figure 2. Correlation between baPWV and IMA in hemodialysis patients. Each dot indicates a one patient. There was a positive correlation between baPWV and IMA. baPWV indicates brachial-ankle pulse wave velocity; and IMA, ischemia-modified albumin.
els compared with those with normal baPWV, no significant difference was found in the multiple linear regression analysis for baPWV. This is possibly because both SBP and glucose had no impact on IMA levels in hemodialysis patients.

There were some limitations in the current study. First, although we estimated the inflammation and oxidative statuses of the hemodialysis patients by measuring hsCPR and SOD, there was still not enough direct evidence to show that inflammation and oxidative stress influenced IMA and thus arterial stiffness. Second, the number of patients was relatively small and therefore larger scale studies are required to verify our findings.

Conclusion

There is a significant association between IMA and arterial stiffness. IMA is a good predictive marker of arterial stiffness in hemodialysis patients.

Disclosure

Conflicts of interest: None.

References

1. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of kidney disease in the United States. Am J Kidney Dis 2016; 67: S1-305.
2. Georgianos PI, Sarafidis PA, Lasaridis AN. Arterial stiffness: a novel cardiovascular risk factor in kidney disease patients. Curr Vasc Pharmac 2015; 13: 229-38.
3. Sarafidis PA, Loutradis C, Karpetas A, et al. Ambulatory pulse wave velocity is a stronger predictor of cardiovascular events and all-cause mortality than office and ambulatory blood pressure in hemodialysis patients. Hypertension 2017; 70: 148-57.
4. Kato A, Takita T, Furuhashi M, Maruyama Y, Miyajima H, Kumagai H. Brachial-ankle pulse wave velocity and the cardiovascular risk index as a predictor of cardiovascular outcomes in patients on regular hemodialysis. Ther Apher Dial 2012; 16: 232-41.
5. Korjian S, Daaboul Y, El-Ghoul B, et al. Change in pulse wave velocity and short-term development of cardiovascular events in the hemodialysis population. J Clin Hypertens (Greenwich) 2016; 18: 857-63.
6. Ma Y, Zhou L, Dong J, Zhang X, Yan S. Arterial stiffness and increased cardiovascular risk in chronic kidney disease. Int Urol Nephrol 2015; 47: 1157-64.
7. Kass DA, Shapiro EP, Kawaguchi M, et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation 2001; 104: 1464-70.
8. Demuth K, Blacher J, Guerin AP, et al. Endothelin and cardiovascular remodelling in end-stage renal disease. Nephrol Dial Transplant 1998; 13: 375-83.
9. Verbeke FH, Agharazii M, Boutouyrie P, Pannier B, Guerin AP, London GM. Local shear stress and brachial artery functions in end-stage renal disease. J Am Soc Nephrol 2007; 18: 621-8.
10. Utescu MS, Couture V, Mac-Way F, et al. Determinants of progression of aortic stiffness in hemodialysis patients: a prospective longitudinal study. Hypertension 2013; 62: 154-60.
11. Chawla R, Goyal N, Calton R, Goyal S. Ischemia modified albumin: a novel marker for acute coronary syndrome. Indian J Clin Biochem 2006; 21: 77-82.
12. Su X, Zhang K, Guo F, et al. Ischemia-modified albumin, a predictive marker of major adverse cardiovascular events in continuous ambulatory peritoneal dialysis patients. Clin Biochem 2013; 46: 1410-3.
13. Sharma R, Gaze DC, Pellerin D, et al. Ischemia-modified albumin predicts mortality in ESRD. Am J Kidney Dis 2006; 47: 493-502.
14. Cengiz H, Dagdeviren H, Kanawati A, et al. Ischemia-modified albumin as an oxidative stress biomarker in early pregnancy loss. J Matern Fetal Neonatal Med 2016; 29: 1754-7.
15. Duarte MM, Rocha JB, MoreSCO RN, et al. Association between ischemia-modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin Biochem 2009; 42: 666-71.
16. Gigante A, Mario F, Barbano B, et al. Nutritional status and intrarenal arterial stiffness in cardiorenal syndrome: a pilot study. Eur Rev Med Pharmacol Sci 2017; 21: 313-6.
17. Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res 2002; 25: 359-64.
18. Yamashina A, Tomiyama H, Arai T, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. Hypertens Res 2003; 26: 615-22.
19. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000; 19: 311-5.
20. Ohyama Y, Ambale-Venkatesh B, Noda C, et al. Aortic arch pulse wave velocity assessed by magnetic resonance imaging as a predictor of incident cardiovascular events: The MESA (Multi-Ethnic Study of Atherosclerosis). Hypertension 2017; 70: 524-30.
21. Kato A. Arterial stiffening and clinical outcomes in dialysis patients. Pulse (Basel) 2015; 3: 89-97.
22. Hendriks EJ, Beulens JW, de Jong PA, et al. Calcification of the splenic, iliac, and breast arteries and risk of all-cause and cardiovascular mortality. Atherosclerosis 2017; 259: 120-7.
23. Utescu MS, Couture V, Mac-Way F, et al. Determinants of progression of aortic stiffness in hemodialysis patients: a prospective longitudinal study. Hypertension 2013; 62: 154-60.
24. Dominguez-Rodriguez A, Abreu-Gonzalez P. Current role of ischemia-modified albumin in routine clinical practice. Biomarkers 2010; 15: 655-62.
Ischemia modified albumin is a sensitive marker of myocardial ischemia after percutaneous coronary intervention. Circulation 2003; 107: 2403-5.

26. Kotani K, Kimura S, Gugliucci A. Paraoxonase-1 and ischemia-modified albumin in patients with end-stage renal disease. J Physiol Biochem 2011; 67: 437-41.

27. Çavuşoğlu Y, Korkmaz Ş, Demirtaş S, et al. Ischemia-modified albumin levels in patients with acute decompensated heart failure treated with dobutamine or levosimendan: IMA-HF study. Anatol J Cardiol 2015; 15: 611-7.

28. Kumar PA, Subramanian K. The role of ischemia modified albumin as a biomarker in patients with chronic liver disease. J Clin Diagn Res 2016; 10: BC09-12.

29. Da Silveira RA, Hermes CL, Almeida TC, et al. Ischemia-modified albumin and inflammatory biomarkers in patients with prostate cancer. Clin Lab 2014; 60: 1703-8.

30. Ulu SM, Yüksel S, Altuntaş A, et al. Associations between serum hepcidin level, FGF-21 level and oxidative stress with arterial stiffness in CAPD patients. Int Urol Nephrol 2014; 46: 2409-14.

31. Desjardins MP, Sidibé A, Fortier C, et al. Association of interleukin-6 with aortic stiffness in end-stage renal disease. J Am Soc Hypertens 2018; 12: 5-13.

32. Salvi P, Parati G. Aortic stiffness and myocardial ischemia. J Hypertens 2015; 33: 1767-71.

33. Whitehouse MW, Walker WR. Copper and inflammation. Agents Actions 1978; 8: 85-90.

34. Milacic V, Chen D, Giovagnini L, Diez A, Fregona D, Dou QP. Pyrrolidine dithiocarbamate-zinc(II) and -copper(II) complexes induce apoptosis in tumor cells by inhibiting the proteasomal activity. Toxicol Appl Pharmacol 2008; 231: 24-33.

35. Hamulakova S, Poprac P, Jomova K, et al. Targeting copper(II)-induced oxidative stress and the acetylcholinesterase system in Alzheimer’s disease using multifunctional tacrine-coumarin hybrid molecules. J Inorg Biochem 2016; 161: 52-62.

36. Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. Oxid Med Cell Longev 2010; 3: 109-21.

37. Bar-Or D, Curtis G, Rao N, Bampos N, Lau E. Characterization of the Co(2+) and Ni(2+) binding amino-acid residues of the N-terminus of human albumin. An insight into the mechanism of a new assay for myocardial ischemia. Eur J Biochem 2001; 268: 42-7.

38. Gaze DC. Ischemia modified albumin: a novel biomarker for the detection of cardiac ischemia. Drug Metab Pharmacokinet 2009; 24: 333-41.

39. Upala S, Wirunsawanya K, Jaruvongvanich V, Sanguankeo A. Effects of statin therapy on arterial stiffness: a systematic review and meta-analysis of randomized controlled trial. Int J Cardiol 2017; 227: 338-41.