Association of plasma bone morphogenetic protein-4 levels with arterial stiffness in hypertensive patients

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Abstract

**Background:** Arterial stiffness interacts with hypertension, becoming an early marker of hypertension-mediated target organ damage. This study aimed to assess the association between plasma concentrations of bone morphogenetic protein-4 (BMP-4) and arterial stiffness during hypertension.

**Methods:** Using cardio-ankle vascular index (CAVI) to determine arterial stiffness status, 204 individuals with essential hypertension were classified into two groups, high CAVI (abnormal) group (n = 94) and low (normal) CAVI group (n = 110). Data were collected including clinical characteristics and laboratory measurements. Plasma levels of BMP-4 were tested by using ELISA analysis.

**Results:** Plasma levels of BMP-4 were substantially greater in high CAVI group than that in low CAVI group [38.51 (31.79–50.83) pg/mL vs. 31.15 (29.38–32.37) pg/mL; p < 0.001]. As shown by spearman correlation analysis, BMP-4 concentrations were correlated with CAVI values in hypertensive individuals (r = 0.406, p < 0.001). After adjustment for potential confounders, elevated BMP-4 levels were related with high CAVI (OR, 1.070; 95% CI, 1.003–1.108; p < 0.001). The best BMP-4 cutoff value for identifying high CAVI, as determined by ROC curve analysis, was 33.34 pg/mL (AUC, 0.751; 95% CI, 0.683–0.818; p < 0.001).

**Conclusion:** Plasma levels of BMP-4 are increased in hypertensive individuals with high CAVI. Elevated BMP-4 levels are strongly correlated with higher CAVI values, implying a predictive value of BMP-4 in arterial stiffness during hypertension.

**KEYWORDS**
arterial stiffness, biomarker, bone morphogenetic protein-4, cardio-ankle vascular index, hypertension

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1  |  INTRODUCTION

Hypertension is considered a risk factor for cardiovascular events. Despite great efforts to reduce hypertension-related all-cause mortality, the prevalence of hypertension continues to increase in developing countries, including China. Arterial stiffness is one of the common vascular complications that increase cardiovascular risks in hypertensive patients. Various processes contribute to the development of arterial stiffness, including renin-angiotensin-aldosterone system (RAAS) activation, inflammation, vascular calcification, adipokines, and insulin resistance.

The bone morphogenetic proteins (BMPs) are initially identified as important signaling molecules in bone formation and now are emerging as crucial players in the regulation of function in multiple tissues and organs. The BMP family and related ligands are subdivided into at least four groups based on sequence similarity, and affinities for specific receptors; the BMP2/4 subgroup; the BMP5-7 subgroup; the BMP9/10 subgroup and the growth and differentiation factor 5–7 subgroup. BMP-4 is predominantly expressed in tissues and organs. The BMP family and related ligands are emerging as crucial players in the regulation of function in multiple tissues and organs. Hypertension is considered a risk factor for cardiovascular events. With the development of arterial stiffness, including renin-angiotensin-aldosterone system (RAAS) activation, inflammation, vascular calcification, adipokines, and insulin resistance.

The bone morphogenetic proteins (BMPs) are initially identified as important signaling molecules in bone formation and now are emerging as crucial players in the regulation of function in multiple tissues and organs. The BMP family and related ligands are subdivided into at least four groups based on sequence similarity, and affinities for specific receptors; the BMP2/4 subgroup; the BMP5-7 subgroup; the BMP9/10 subgroup and the growth and differentiation factor 5–7 subgroup. BMP-4 is predominantly expressed in endothelial cells and can be induced by oscillatory shear stress in the early stage of atherosclerosis. Mounting evidence suggested that BMP-4 is an essential regulator in cardiovascular homeostasis and disorders and functions as a proinflammatory, prooxidant, prohypertensive, and proatherogenic mediator in systemic arteries. Specifically, BMP-4 plays critical roles in the occurrence and development of hypertension. Chronic infusion of BMP-4 generated considerable and increasing hypertension in mice through elevating the levels of vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and the resulting overproduction of reactive oxygen species. This disrupted endothelial function in hypertensive mice.

There are limited studies investigating whether the levels of circulating BMP-4 in humans signify the commencement of early atherosclerosis. Recent studies found that plasma BMP-4 levels were enhanced after resuscitation. Interestingly, serum concentrations of BMP-4 were strongly correlated with the likelihood of developing left ventricular hypertrophy in individuals with hypertension while being negatively correlated with carotid atherosclerosis in individuals with diabetes mellitus. However, the specific roles of BMP-4 in arterial stiffness among patients who suffer from hypertension and atherosclerosis remain largely unclear. This work sought to evaluate the association between BMP-4 and cardio-ankle vascular index (CAVI) as a new measurement of arterial stiffness in hypertension.

2  |  MATERIALS AND METHODS

2.1  |  Patients

Participants of this study were hypertensive patients aged 18 years or above, recruited from the Department of Geriatrics ward in Beijing Tongren Hospital Affiliated to Capital Medical University between June 2021 and May 2022. Systolic blood pressure (SBP) or diastolic blood pressure (DBP) reading above 140/90 mmHg, any use of antihypertensive drugs, or a self-reported history of hypertension, was considered hypertension. Based on the readings of the patient’s blood pressure, hypertension was further divided into three grades: grade 1, grade 2, and grade 3. Grade 1 was defined as SBP between 140 and 159 mmHg or DBP between 90 and 99 mmHg. Grade 2 was described as having an SBP of between 160 and 179 mmHg or a DBP of between 100 and 109 mmHg, and Grade 3 was considered to have an SBP of more than 180 mmHg or a DBP of more than 110 mmHg. Following was a list of the exclusion criteria: secondary hypertension, chronic heart failure, acute coronary syndrome, peripheral arterial disease, atrial fibrillation, cerebrovascular illness (including stroke and transient ischemic attack), chronic kidney disease (estimated glomerular filtration rate [eGFR] < 45 ml/min/1.73 m²), calculated using the CKD-EPI formula), ankle-brachial index ≥ 0.9, acute infectious diseases, autoimmune diseases, and malignant neoplasms. This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans after receiving approval from the Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University (No. TRECKY 2021–172).

2.2  |  Data collection

All patients’ age, gender, cigarette use, alcohol consumption, duration of hypertension, blood pressure grading, history of diabetes mellitus, dyslipidemia, coronary heart disease, and hyperuricemia, as well as their medication history, were gathered from their comprehensive medical records. Smoking history was defined as participants who have smoked at least 20 packets of cigarettes in their lifetime and currently smoke cigarettes. Drinking history was defined as consuming at least one drink per month for a year.

All measurements were performed using standardized equipment. On admission, skilled nurses measured the patient’s height, weight, blood pressure, heart rate, and body mass index (BMI; calculated as weight [kg]/height squared [m²]). Blood pressure and heart rate were measured with a newly calibrated device with a digital readout (Omron HEM-7051, Tokyo, Japan). Patients should be seated for at least 5 min in a quiet room before blood pressure measurements and keep the upper arm at the heart level. The average of two blood pressure readings was recorded.

Biochemical tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-sensitivity C-reactive protein (hs-CRP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), creatinine, blood urea nitrogen (BUN), uric acid (UA), lipide profiles including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and lipoprotein (a) (LP (a)). Urine from the first void was analyzed to calculate the albumin to creatinine ratio. The level of HbA1c was determined using the fully automatic glycohemoglobin analyzer (HCL-723G8, SYSMEX, Japan). Other blood samples were measured using the automatic biochemical analyzer (AU5821,
Plasma levels of BMP-4 were markedly elevated in hypertensive patients with high CAVI compared with those of low CAVI [38.51 (31.79–50.83) pg/mL vs. 31.15 (29.38–32.37) pg/mL; \( p < 0.001 \); Figure 1]. Correlation analysis indicated that plasma BMP-4 concentrations were substantially linked with CAVI levels in hypertensive patients \( (r = 0.406, p < 0.001, \text{Figure 2}) \).
| Variables                              | High (abnormal) CAVI ($n = 94$) | Low (normal) CAVI ($n = 110$) | $p$ value |
|----------------------------------------|----------------------------------|--------------------------------|-----------|
| Age (year)                             | 66.40 ± 13.40                    | 65.70 ± 12.06                  | 0.693     |
| Male, n (%)                            | 58 (61.70)                       | 70 (63.64)                     | 0.776     |
| Body mass index (kg/m$^2$)             | 24.22 (23.12–26.81)              | 25.46 (23.77–27.55)            | 0.036     |
| Smoking, n (%)                         | 87 (92.55)                       | 87 (79.09)                     | 0.007*    |
| Drinking, n (%)                        | 78 (82.98)                       | 80 (72.73)                     | 0.081     |
| Duration of hypertension (year)        | 13.50 (9.00–21.00)               | 10.00 (5.50–20.00)             | 0.097     |
| Blood pressure grading                 |                                  |                                | 0.340     |
| Grade 1, n (%)                         | 7 (7.45)                         | 8 (7.27)                       |           |
| Grade 2, n (%)                         | 25 (26.60)                       | 20 (18.18)                     |           |
| Grade 3, n (%)                         | 62 (65.96)                       | 82 (74.55)                     |           |
| Clinical comorbidity                   |                                  |                                |           |
| Diabetes mellitus, n (%)               | 49 (52.13)                       | 53 (48.18)                     | 0.574     |
| CHD, n (%)                             | 27 (28.72)                       | 14 (12.73)                     | 0.004*    |
| Dyslipidemia, n (%)                    | 60 (63.83)                       | 69 (62.73)                     | 0.871     |
| Hyperuricemia, n (%)                   | 13 (13.82)                       | 17 (15.45)                     | 0.744     |
| Laboratory data                        |                                  |                                |           |
| FBG (mmol/L)                           | 5.82 (5.21–7.20)                 | 5.74 (5.00–6.80)               | 0.376     |
| HbA1c (%)                              | 6.15 (5.70–7.25)                 | 5.90 (5.60–6.95)               | 0.272     |
| BUN (mmol/L)                           | 5.40 (4.80–6.30)                 | 5.30 (4.30–6.20)               | 0.232     |
| Creatinine (μmol/L)                    | 72.00 (60.20–82.00)              | 70.30 (61.50–80.20)            | 0.541     |
| eGFR (ml/min/1.73 m$^2$)               | 77.04 ± 16.09                    | 86.83 ± 17.71                  | <0.001**  |
| Uric acid (μmol/L)                     | 341.00 (298.00–410.00)           | 346.00 (288.20–393.90)         | 0.911     |
| ALT (U/L)                              | 17.00 (13.00–25.00)              | 19.50 (13.00–28.00)            | 0.361     |
| AST (U/L)                              | 19.00 (17.00–23.00)              | 20.00 (17.00–24.00)            | 0.612     |
| Hs-CRP (mg/L)                          | 0.75 (0.40–3.00)                 | 0.90 (0.50–2.20)               | 0.651     |
| Lipoprotein (a) (mg/dL)                | 11.00 (4.30–26.30)               | 9.80 (3.90–31.20)              | 0.888     |
| TG (mmol/L)                            | 1.41 (0.96–2.02)                 | 1.27 (0.92–1.70)               | 0.296     |
| TC (mmol/L)                            | 4.12 (3.51–5.15)                 | 4.58 (3.84–5.38)               | 0.120     |
| LDL-C (mmol/L)                         | 2.33 (1.83–3.33)                 | 2.75 (2.01–3.40)               | 0.184     |
| HDL-C (mmol/L)                         | 1.17 (0.94–1.43)                 | 1.19 (0.99–1.48)               | 0.417     |
| ACR (mg/g)                             | 6.71 (3.71–21.97)                | 4.40 (2.98–14.21)              | 0.205     |
| BMP-4 (pg/mL)                          | 38.51 (31.79–50.83)              | 31.15 (29.38–32.37)            | <0.001**  |
| CAVI                                   | 9.93 (9.30–10.95)                | 8.05 (7.50–8.40)               | <0.001**  |
| SBP (mmHg)                             | 132.73 ± 17.21                   | 133.81 ± 15.01                 | 0.636     |
| DBP (mmHg)                             | 75.40 ± 9.34                     | 77.83 ± 9.55                   | 0.068     |
| Heart rate (bpm)                       | 71.02 ± 11.04                    | 72.22 ± 9.47                   | 0.416     |
| Medications, n (%)                     |                                  |                                |           |
| Antihypertensive agents                | 33 (35.11)                       | 40 (36.36)                     | 0.852     |
| Antiplatelet agents                    | 31 (32.98)                       | 22 (22.00)                     | 0.035*    |
| Antilipemic agents                     | 53 (56.38)                       | 56 (50.91)                     | 0.435     |
| Antidiabetic agents                    | 42 (44.68)                       | 42 (38.18)                     | 0.347     |

Note: Data are given as mean ± standard deviation, median (25th and 75th percentiles) or valid percentages ($n$%). * $p < 0.05$. ** $p < 0.001$.

Abbreviations: ACR, albumin/creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMP-4, bone morphogenetic protein-4; BUN, blood urea nitrogen; CAVI, cardio-ankle vascular index; CHD, coronary heart disease; DBP, diabolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
3.3 | The association between plasma BMP-4 levels and high CAVI in hypertensive individuals

As seen in Figure 3, Univariate logistic regression analysis revealed that higher levels of BMP-4 were notably linked with high CAVI in hypertensive individuals (OR, 1.073; 95% CI, 1.038–1.110; p < 0.001). After adjusting for gender, age, BMI, duration of hypertension, smoking, diabetes mellitus, dyslipidemia, coronary heart disease, and the use of antiplatelet medications, the concentration of BMP-4 remained substantially linked with high CAVI in hypertensive individuals (OR, 1.070; 95% CI, 1.033–1.108; p < 0.001). Figure 4 illustrates the ROC curve for the BMP-4 to distinguish high CAVI and low CAVI in hypertension. BMP-4’s area under the curve was calculated to be 0.751 (95% CI, 0.683–0.818; p < 0.001). The best BMP-4 cutoff value for detecting high CAVI in hypertensive individuals was 33.34 pg/mL, in which the sensitivity was 66.0%, and the specificity was 78.2%.

4 | DISCUSSION

In current work, we demonstrated, for the first time, that plasma BMP-4 levels are positively associated with high CAVI in hypertensive patients, after adjusting for potential confounders. Furthermore, the ROC curve analysis revealed that BMP-4 could predict increased...
arterial stiffness in hypertensive individuals, indicating a substantial role for BMP-4 in the atherosclerosis process in the hypertensive population.

Arterial stiffness increases with age, as well as in various pathological status, such as obesity, smoking, diabetes mellitus, dyslipidemia, and hypertension. It is becoming increasingly important in clinical applications as an early indicator of hypertension-mediated targeted organ damage and is being thought as a potential therapeutic marker in hypertensive patients. There have been a number of mechanisms including vascular inflammation, vascular calcification, activation of RAAS, increased oxidative stress, insulin resistance, and adipokines, which ultimately result in artery stiffening. In our present study, we had considered the effects of age, diabetes mellitus, dyslipidemia, smoking, and obesity assessed by BMI on arterial stiffness. After adjusting for the above potential confounders, the levels of BMP-4 remained significantly associated with high (abnormal) CAVI in hypertensive individuals.

The BMP family, initially identified as important signaling molecules in bone formation, now are emerging as crucial players in the regulation of function in multiple tissues and organs. BMP-4, induced by oscillatory shear stress and predominantly expressed in endothelial cells, is one of the common triggers for endothelial dysfunction in hypertension. A rising body of evidence indicates that BMP-4 has proinflammatory and prooxidant properties in systemic arteries, implying that BMP-4 signaling is crucial in the cardiovascular homeostasis and disorders, including hypertension, atherosclerosis, and cardiac dysfunction. However, studies investigating the relationship between BMP-4 levels and arterial stiffness in the hypertension population are sparse.

Patients who had survived a cardiac arrest outside of a hospital exhibited greater plasma levels of BMP-4 in comparison to those who had coronary artery disease or healthy volunteers. Circulating BMP-4 levels were similarly raised following surgery and were closely correlated with inflammation cytokines. This rise in circulating BMP-4 may be alleviated by flurbiprofen, implying that BMP-4 exerts proinflammatory features through the cyclooxygenase-II signaling pathway. Recent studies indicate that BMP-4 may be able to cause left ventricular hypertrophy in hypertensive patients. Our present results showed that plasma concentrations of BMP-4 were elevated in hypertensive individuals with high CAVI than those with low CAVI and were positively correlated with the CAVI values, implying that BMP-4 might become a novel biomarker for arterial stiffness and early atherosclerosis. These findings are partially consistent with the findings of previous studies.

Nevertheless, there are still controversial for impacts of BMP4 on cardiorenal system. BMP-4 levels were inversely related to carotid atherosclerosis, and individuals with diabetes mellitus had lower serum concentrations of both BMP-4 and the antagonist noggin. It was postulated that once the levels of BMP-4 begin to increase, the concentrations of its antagonists may also start to rise to counterbalance the action of BMP-4. Individuals who suffered from chronic kidney disease (CKD) and coronary artery disease had increased serum levels of BMP-4, whereas patients without CKD did not vary from one another in this regard. This situation may be explained by an accumulation of BMP-4 in the atherosclerotic vascular tissue, as suggested by the minimal study that has been done on the subjects.

It is unknown how exactly increased BMP-4 causes arterial stiffness in the hypertensive population since the particular mechanism responsible for this effect remains unknown. This study indicated that the risk of abnormal CAVI increased with plasma levels of BMP-4, even after accounting for other variables that may be associated. Arterial stiffness may be caused by a number of conditions, including age, smoking, obesity, and many more. Given this, an increase in arterial stiffness cannot directly reflect the control of blood pressure management and the improvement of medication therapy in hypertensive individuals, of which clinical application is limited. When further ROC analysis was performed on the data from this study, it was shown that when the concentration of BMP-4 reached the cut-off value of 33.34 pg/mL, the test had high sensitivity and specificity for identifying and diagnosing increased arterial stiffness. Not only might BMP-4 be used as an indicator for increased arterial stiffness in the hypertensive population and as a monitoring index for the improvement of hypertension-related subclinical events, which has a specific clinical application value.

This current study has several limitations that must be considered. First, the subjects were selected among hospitalized patients, which may have caused a selection bias. Second, since this was a cross-sectional study, it is impossible to determine the causal link with certainty. Finally, the sample size of the study was also somewhat limited. Therefore, more extensive prospective studies are needed to provide more confirmation.

5 | CONCLUSIONS
In conclusion, plasma levels of BMP-4 are elevated in hypertensive individuals with high CAVI. The increase of BMP-4 is independently associated with higher CAVI values in patients with hypertension, implying that plasma BMP-4 levels may serve as a predictive indicator of arterial stiffness in hypertensive individuals. Defining BMP-4 as a new biomarker might help stratify the cardiovascular risk and offer potential therapeutic strategies for arterial stiffness. Clarifying the precise functions and underlying processes of BMP-4 in arterial stiffness during hypertension calls for more studies.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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