Serum adipocyte fatty acid-binding protein level is positively associated with aortic stiffness in nondialysis chronic kidney disease patients

A cross-sectional study

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Abstract

Aortic stiffness (AS) is a major predictor of cardiovascular disease and mortality in patients with chronic kidney disease (CKD) and adipocyte fatty acid-binding protein (A-FABP) is a novel adipokine that is positively correlated with AS in the general population. Therefore, we investigated the correlation between serum A-FABP levels and AS in nondialysis CKD patients.

Fasting blood samples and baseline characteristics were obtained in 270 patients with nondialysis CKD. Serum A-FABP concentrations were determined by enzyme immunoassay and carotid-femoral pulse wave velocity (cfPWV) measurements were acquired using a validated tonometry system. Patients with cfPWV >10 m/s formed the AS group, while those with values ≤10 m/s comprised the comparison group.

Among 270 CKD patients, 92 patients (34.1%) were in the AS group. Compared to those in the comparison group, patients in the AS group were older (\(P < .001\)), had a higher prevalence of diabetes, along with higher serum A-FABP level (\(P < .001\)), larger waist circumference (\(P = .004\)), and lower estimated glomerular filtration rate (\(P = .001\)) but higher levels of body fat mass (\(P = .010\)), systolic blood pressure (\(P < .001\)), fasting glucose (\(P = .014\)), blood urea nitrogen (\(P = .009\)), and serum creatinine (\(P = .004\)). The serum log-A-FABP level was positively associated with log-cfPWV (\(β = 0.178, P = .001\)) in nondialysis CKD patients and multivariable logistic regression analysis identified serum A-FABP (\(P = .006\)), age (\(P = .001\)), and systolic blood pressure (\(P = .015\)) as independent predictors of AS in nondialysis-dependent CKD patients.

Elevated A-FABP levels may be a significant predictor of AS in nondialysis CKD patients.

Abbreviations: A-FABP = adipocyte fatty acid-binding protein, AS = aortic stiffness, BUN = blood urea nitrogen, cfPWV = carotid–femoral pulse wave velocity, CI = confidence interval, CKD = chronic kidney disease, Cre = creatinine, CVD = cardiovascular disease, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FPG = fasting plasma glucose, IQR = interquartile range, JNK = Jun NH2-terminal kinase, LDL-C = low-density lipoprotein cholesterol, NF-κB = nuclear factor kappa B, OR = odds ratio, SBP = systolic blood pressure, SPSS = statistical package for the social sciences, TCH = total cholesterol, TGs = triglycerides.

Keywords: adipocyte fatty acid-binding protein, aortic stiffness, cardiovascular disease, carotid–femoral pulse wave velocity, chronic kidney disease, vascular calcification

1. Introduction

The incidence of chronic kidney disease (CKD) has increased worldwide and is regarded as a main public health concern in the world. Progressive CKD leads to a higher prevalence of cardiovascular disease (CVD) due to aortic stiffness (AS), caused by atherosclerosis and arteriosclerosis.\(^1\)

Indeed, increased AS and intima-media thickness are the hallmarks of arterial alterations among CKD patients.\(^2\) Although multidisciplinary strategies have been used to alter the pathophysiology of atherosclerosis and vascular calcification, cardiovascular risk among this population remains high.\(^3\)

Adipocyte fatty acid-binding protein (A-FABP) is a cytoplasmic lipid-binding protein that is mainly expressed in adipocytes and macrophages.\(^4\) It is a key regulator of glucose and lipid metabolism that is related to inflammatory and metabolic

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processes implicated in the pathophysiology of atherosclerosis in the general population. Previous studies have shown that serum A-FABP levels were positively correlated with AS in patients with type II diabetes mellitus (DM), hypertension and metabolic syndrome, and in the geriatric population. Serum A-FABP levels are also an important predictor of not only coronary artery disease but also progression of carotid atherosclerosis in the general population and in patients with end-stage renal disease (ESRD)\(^{[6,7]}\); however, it is not known if this correlation applies to nondialysis CKD patients. Therefore, this study aimed to assess the relationship between serum A-FABP levels and AS, measured by carotid–femoral pulse wave velocity (cfPWV), among nondialysis CKD patients.

2. Methods

2.1. Participants

Between January and December, 2016, we conducted a cross-sectional study in the renal outpatient department of a medical center in Hualien, Taiwan. The Protection of Human Subjects Institutional Review Board at the Tzu Chi Hospital approved this study. Written informed consent was obtained from each patient before they were recruited. All of the patients from renal outpatient department who aged 20 years or more with documented CKD and not needing dialysis according to the KDIGO guidelines were invited to participate in the study. Patients with acute infection, malignancy, stroke, heart failure, acute coronary syndrome, or amputation, and those who refused to provide informed consent were excluded from the study. A total of 270 nondialysis CKD patients were enrolled, and demographic and medical data of the participants, including prevalence of DM, hypertension, and glomerulonephritis, were retrieved from electronic medical records.

2.2. Anthropometric analysis

Body weight and height were measured with patients wearing light clothing and without shoes. Body mass index was calculated as the weight in kilograms divided by the height in meters squared. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Body fat mass was measured using a single-frequency (50 kHz) standard tetrapolar whole body bioimpedance analyzer (Biodynamic-450, Biodynamics Corporation, Seattle) in the supine position and computed using specific formulas supplied by the manufacturer.

2.3. Biochemical investigations

Overnight fasting blood samples (approximately 5 mL) were obtained from all participants and immediately centrifuged at 3000 g for 10 minutes. Serum levels of blood urea nitrogen (BUN), creatinine (Cre), fasting plasma glucose (FPG), total cholesterol (TCH), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and total calcium and phosphorus were determined using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany). Serum A-FABP (catalog number: A05181S, PI-BIO, Montigny le Bretonneux, France) concentration was measured using a commercially available enzyme immunoassay.\(^{[6,7]}\) Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

2.4. Measurement of blood pressure and cfPWV

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in all participants in the morning with standard sphygmomanometers and after they had rested for at least 10 minutes. Blood pressure was measured thrice at 5-minute intervals and averaged data were used for analysis. Applanation tonometry (SphygmoCor system, AtCor Medical, Australia) was used to measure cfPWV, a well-established parameter of AS and predictor of cardiovascular risk, by transcutaneously recording the pressure pulse waveform in the underlying artery. Detailed procedure for using this device has been described by us elsewhere.\(^{[6,7,10]}\) Measurements were acquired in the morning and after the participants had rested in the supine position for at least 10 minutes. Based on the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines, we used a cfPWV cutoff value of 10 m/s to define high or low arterial stiffness groups.\(^{[6,7]}\)

2.5. Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. The Kolmogorov–Smirnov test was used to determine data distribution patterns. Normally distributed data are expressed as means ± standard deviation, and Student independent t-test (two-tailed) was used for comparisons between-group. Nonnormally distributed data are expressed as median and interquartile range (IQR), and the Mann–Whitney U test was used for comparison (cfPWV, TGs, LDL-C, FPG, BUN, Cre, and A-FABP). Categorical data were analyzed by the χ²-test and data are presented as numbers and percentages. Variables that were significantly associated with AS in univariable analysis were tested for independence by multivariable logistic regression analysis (adapted factors: DM, age, body fat mass, waist circumference, SBP, FPG, BUN, Cre, eGFR, and A-FABP). Given that cfPWV, TGs, LDL-C, FPG, BUN, Cre, and A-FABP were not normally distributed, base 10 logarithmic transformations to achieve normality were calculated and used for analysis. Variables that were significantly associated with cfPWV values in patients with nondialysis CKD were subjected to linear regression analysis and subsequent multivariable forward stepwise regression analysis. A receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC) to identify the value of those significant variables predicting AS in patients with nondialysis CKD by logistic regression. \(P < .05\) was considered statistically significant.

3. Results

3.1. Baseline demographics and clinical characteristics of nondialysis CKD patients

Clinical characteristics of the 270 study participants are presented in Table 1; of these, 92 (34.1%) were classified in the AS group, and others in the comparison group. Compared to those in the comparison group, patients in the AS group were older (\(P < .001\)), had a higher prevalence of DM (\(P = .004\)) but lower eGFR (\(P = .001\)), along with greater serum A-FABP levels (\(P < .001\)), larger waist circumference (\(P = .004\)), and higher levels of body fat mass (\(P = .010\)), SBP (\(P < .001\)), FPG (\(P = .014\)), BUN (\(P = .009\)), and Cre (\(P = .004\)). There were no significant differences between the 2 groups in sex ratio, comorbidities associated with hypertension, or chronic glomerulonephritis.

3.2. Correlation between AS and clinical variables

Adjustment of factors significantly associated with AS (DM, age, body fat mass, waist circumference, SBP, FPG, BUN, Cre, eGFR, and A-FABP) in multivariable logistic regression analysis revealed that serum A-FABP level (odds ratio [OR] 1.044, 95% confidence interval [CI] 1.047–1.317, \(P = .006\)), age (OR 1.062, 95% CI 1.033–1.092, \(P < .001\)), and SBP (OR 1.017, 95% CI 1.003–1.031, \(P = .015\)) were independent predictors of AS in nondialysis CKD patients (Table 2).
variables associated with logarithmically transformed cfPWV

Data on simple and multivariable linear analyses of clinical log-cfPWV in nondialysis CKD patients

3.3. Log-A-FABP level is independently associated with log-cfPWV in nondialysis CKD patients

Data on simple and multivariable linear analyses of clinical variables associated with logarithmically transformed cfPWV (log-cfPWV) values are presented in Table 3. DM (β = 0.206, P < .001), age (β = 0.395, P < .001), and A-FABP level (β = 0.252, P < .001) were independently associated with log-cfPWV values (Table 3).

3.4. The diagnostic value of age, SBP, and A-FABP on AS

An ROC analysis was performed to assess the predicting value of those significant variables associated with AS in patients with nondialysis CKD (Table 4). The AUC was 0.688 for age (95% CI: 0.629–0.743, P < .001), 0.638 for SBP (95% CI: 0.576–0.696, P < .001), and 0.694 for the A-FABP level (95% CI: 0.636–0.749, P < .001). Furthermore, the AUC of those variables’ combination revealed that age with SBP: 0.728 (95% CI: 0.671–0.780), age with A-FABP: 0.753 (95% CI: 0.697–0.803), SBP with A-FABP: 0.715 (95% CI: 0.657–0.768), age, SBP, and A-FABP: 0.762 (95% CI: 0.706–0.811), with all P < .001. The AUC value of A-FABP is higher than that of age and SBP; in addition, the combination of these variables has higher AUC value than any single one.

4. Discussion

The primary finding of this cross-sectional study is that serum A-FABP levels are higher in nondialysis CKD patients with AS than in those without AS, and that A-FABP levels, in addition to age and SBP, are an independent predictor of AS in this population. The diagnostic power estimated by AUC at predicting AS in nondialysis CKD patients is better in A-FABP level than age or SBP; moreover, the diagnostic performance is even superior in combination of all 3 significant variables. Furthermore, log-serum-A-FABP levels are positively associated with log-cfPWV values.
Table 3

Correlation between carotid–femoral pulse wave velocity levels and clinical variables among the 270 chronic kidney disease patients.

| Variables                        | Simple linear regression | Multivariable linear regression |
|----------------------------------|--------------------------|---------------------------------|
|                                  | r                        | P value | Beta             | Adjusted R² change | P value |
| Female                           | −0.123                   | .043*   | −0.110           | 0.009              | .037*   |
| Diabetes mellitus                | 0.226                    | <.001*  | 0.206            | 0.051              | <.001*  |
| Hypertension                     | 0.069                    | .256    | –                 | –                  | –       |
| Glomerulonephritis               | −0.137                   | .029*   | –                 | –                  | –       |
| Age (years)                      | 0.387                    | <.001*  | 0.395            | 0.147              | <.001*  |
| Height (cm)                      | −0.019                   | .753    | –                 | –                  | –       |
| Body weight (kg)                 | 0.081                    | .186    | –                 | –                  | –       |
| Body mass index (kg/m²)          | 0.101                    | .096    | –                 | –                  | –       |
| Waist circumference (cm)         | 0.234                    | <.001*  | –                 | –                  | –       |
| Body fat mass (%)                | 0.114                    | .062    | –                 | –                  | –       |
| SBP (mmHg)                       | 0.407                    | <.001*  | 0.252            | 0.071              | <.001*  |
| DBP (mmHg)                       | 0.210                    | .01*    | –                 | –                  | –       |
| Log-Creatinine (mg/dL)           | −0.114                   | .062    | –                 | –                  | –       |
| Log-Triglyceride (mg/dL)         | 0.062                    | .310    | –                 | –                  | –       |
| Log-LDL-C (mg/dL)                | −0.111                   | .068    | –                 | –                  | –       |
| Log-Glucose (mg/dL)              | 0.141                    | .020*   | –                 | –                  | –       |
| Log-BUN (mg/dL)                  | 0.180                    | .003*   | –                 | –                  | –       |
| Log-Glomerulonephritis           | 0.220                    | <.001*  | –                 | –                  | –       |
| eGFR (mL/min)                    | −0.284                   | <.001*  | –                 | –                  | –       |
| Log-A-FABP (mg/mL)               | 0.258                    | .01*    | 0.178            | 0.021              | .001*   |

Data of carotid–femoral pulse wave velocity, TCH, triglyceride, LDL-C, glucose, BUN, creatinine, and A-FABP levels showed skewed distribution and therefore were log-transformed before analysis. Analysis of data was done using the univariable linear regression analyses or multivariable stepwise linear regression analysis (adapted factors were female, diabetes mellitus, glomerulonephritis, age, waist circumference, SBP, DBP, log-Glucose, log-BUN, log-Creatinine, eGFR, and log-A-FABP).

A-FABP = adipocyte fatty acid-binding protein, BUN = blood urea nitrogen, cfPWV = carotid–femoral pulse wave velocity, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TCH = total cholesterol.

Table 4

The diagnostic value of age, systolic blood pressure, and adipocyte fatty acid-binding protein on aortic stiffness among 270 chronic kidney disease patients.

| Variables     | AUC (95% CI) | P value |
|---------------|--------------|---------|
| Age, y        | 0.688 (0.629–0.743) | <.001* |
| SBP           | 0.638 (0.578–0.696)  | <.001* |
| A-FABP        | 0.694 (0.636–0.749)  | <.001* |
| Age + SBP     | 0.728 (0.671–0.780)  | <.001* |
| Age + A-FABP  | 0.753 (0.697–0.803)  | <.001* |
| SBP + A-FABP  | 0.715 (0.657–0.768)  | <.001* |
| Age + SBP + A-FABP | 0.762 (0.706–0.811) | <.001* |

A-FABP = adipocyte fatty acid-binding protein, AUC = area under the curve, CI = confidence interval, SBP = systolic blood pressure.

*AUC was significantly different from 0.500.

Aortic stiffening is associated with aging and many diseases such as DM, atherosclerosis, and CKD may accelerate this process. Collagen and elastin are the 2 main scaffolding proteins that contribute to the stability, resilience, and compliance of the vascular wall, and inflammation often causes dysregulation of collagen and elastin, including overproduction of abnormal collagen and/or reduced levels of normal elastin, which further contribute to vascular stiffness. Thus, aging and high SBP are risk factors that are logically expected to accelerate development of AS, as seen in our cohort of nondialysis CKD patients.

Multivariable stepwise linear regression analysis identified older age and higher SBP to be independently associated with log cfPWV values, and if AS is categorized as a surrogate marker of coronary artery disease, knowledge on the harbinger of AS would be valuable. Serum A-FABP has been extensively evaluated as a biomarker of atherosclerotic diseases in the general and geriatric populations and among those with risk factors of atherosclerotic disease such as DM, hypertension, metabolic syndrome, obesity, and CVD. Additionally, serum A-FABP levels are a marker of atherosclerosis and a predictor of cardiovascular mortality in ESRD patients, and our results in nondialysis CKD patients concur with those from previous studies in other populations where higher serum A-FABP was seen in individuals with AS.

Recent studies have proposed several mechanisms to explain how A-FABP can influence metabolic status and to describe its association with vascular dysfunction through direct and indirect effects on adipose–vascular interactions. The first of these involves the activation of A-FABP in response to inflammation due to ER stress via the nuclear factor kappa B (NF-kB) and c-Jun NH2-terminal kinase (JNK) pathways. This direct effect is thought to be responsible for the pathological progression of vasculopathy and lipotoxicity due to enhanced adipocyte insulin resistance. The second mechanism, characterized in mice deficient in apolipoprotein E and A-FABP, is based on a marked reduction in atherosclerotic lesions along the aorta, which was substantiated by the observation that pharmacological inhibition of A-FABP protected the animals against atherosclerotic plaque formation. Taken together, these results indicate that A-FABP itself may have proatherogenic activity. Third, an in vitro study revealed that A-FABP causes endothelial dysfunction due to inhibition of endothelial nitric oxide synthase by A-FABP-induced suppression of insulin receptor substrate 1 and Akt expression. Additionally, chronic low-grade inflammation could result in inhibition of basal NO synthesis, which would lead to endothelial dysfunction, smooth muscle cell proliferation, and changes in the composition of the extracellular matrix. Vascular calcification is also promoted by higher expression of osteoblast markers, inflammation-induced osteogenic phenotype in smooth muscle cells, and downregulation of fetuin-A, an inhibitor of vascular calcification. Moreover, the indirect effects of high serum A-FABP that are associated with adipose–vascular interaction...
also correlate with factors that predict greater risk of CVD and mortality, such as obesity, hypertension, insulin resistance, LDL-C, metabolic syndrome, and type 2 DM. [11,12,23] Thus, these mechanisms lend support to the clinical evidence that A-FABP levels are positively associated with volume of coronary plaques [14,16,21] and also explain our finding that A-FABP has a positive correlation with AS in nondialysis CKD patients.

cfPWV is the gold standard parameter for evaluating AS and arterial function, and is an established prognostic marker of CVD and all-cause mortality. [24,27] A systematic review and meta-analysis has reported a 15% increase in cardiovascular mortality and all-cause mortality for every 1 m/s elevation in aortic PWV. [24] Previous studies have revealed that higher cfPWV values are related to the presence of multiple risk factors, such as age, elevated SBP, and diabetes in CKD patients, along with cross-talk between CVD and A-FABP. [24,25,28–30]

Importantly, our results in nondialysis CKD patients are in agreement with these results as we show that serum log-A-FABP levels are positively associated with log-cfPWV values in this population.

We show that DM is one of the factors that is independently associated with log-cfPWV, which is in agreement with the fact that hyperglycemia can change the composition of the arterial wall and contribute to its stiffness, in addition to its effect on atherogenesis. [31] Mechanistically, hyperglycemia damages the interstitial layer of the arterial wall through the generation of advanced glycated end products that result from nonenzymatic glycation of proteins. [1] Chronic hyperglycemia and hyperinsulinemia also activate the renin-angiotensin-aldosterone system, which results in wall hypertrophy and fibrosis due to overexpression of the angiotensin type I receptor in vascular tissue. [32]

There are several limitations to our study. First, the cross-sectional design could only prove an association between serum A-FABP and AS in nondialysis CKD patients and future long-term prospective studies are needed to establish causality, if any. Second, our nondialysis CKD patients came from a single medical center in Taiwan, who may not be sufficiently representative of other population or ethnicities.

5. Conclusion

We found that the serum A-FABP level was positively correlated with AS in nondialysis CKD patients. Serum log-A-FABP values, elevated SBP, old age, and DM were positively associated, while female gender was negatively associated with log-cfPWV in these patients. Serum A-FABP represents a potentially useful predictive marker of AS in nondialysis CKD patients.

Author contributions

Writing—original draft preparation, methodology: H.-Y.S. Conceptualization, methodology, formal analysis, data curation, funding acquisition, writing—review and editing: B.-G.H. Conceptualization, investigation, formal analysis, data curation, funding acquisition, writing—review and editing, supervision: Y.-H.L.

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