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Original Article

High Serum Adipocyte Fatty Acid Binding Protein Levels Associated with Aortic Stiffness in Geriatric Persons with Type 2 Diabetes Mellitus

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SUMMARY

Background: Adipocyte fatty acid binding protein (A-FABP) plays crucial roles in obesity, insulin resistance, lipid metabolism, inflammation, and atherosclerosis. The present study aimed to evaluate the relationship between fasting serum A-FABP levels and aortic stiffness in geriatric persons with type 2 diabetes mellitus (T2DM).
Methods: General characteristics and fasting serum A-FABP concentrations were measured in 120 geriatric persons with T2DM. Serum A-FABP levels were determined using an enzyme immunoassay kit. A carotid-femoral pulse wave velocity (cfPWV) value > 10 m/s, as determined using the SphygmoCor system, was defined as an indicator of aortic stiffness.
Results: Among the 120 geriatric participants with T2DM, 57 participants (47.5%) were classified in the aortic stiffness group. Systolic blood pressure ($p = 0.031$) and serum A-FABP levels ($p < 0.001$) were higher in the aortic stiffness group than in the control group. Multivariate logistic regression analysis with additional variables also noted A-FABP level (odds ratio: 1.078, 95% confidence interval: 1.032–1.126, $p = 0.001$) was an independent predictors of aortic stiffness in geriatric persons with T2DM. Multivariate forward stepwise linear regression analysis also showed that logarithmically transformed A-FABP levels (log-A-FABP, $\beta = 0.217$, adjusted R^2 change = 0.040, $p = 0.013$) were positively associated with cfPWV values in geriatric persons with T2DM.
Conclusions: Serum A-FABP level is an independent predictor of aortic stiffness and is positively associated with cfPWV values in geriatric persons with T2DM.

1. Introduction

Diabetes mellitus (DM) is a group of abnormal carbohydrate metabolism diseases characterized by hyperglycemia.[1] It is a global public health issue that affected 451 million adults worldwide in 2017, and the incidence is expected to increase to 693 million by 2045. Furthermore, it has been estimated that as much as 50% of all people with diabetes remain undiagnosed.[2] The most common type of diabetes is Type 2 DM (T2DM), which accounts for 90% to 95% of adults diabetes cases.[3] Among these patients, T2DM is most commonly seen in adults ≥ 65 years of age.[2]

Increasing hyperglycemia has a direct correlation with the risk of developing cardiovascular complications.[4] Cardiovascular disease (CVD) is estimated to affect 32.2% of DM patients, making it one of the most common comorbidities of diabetes.[5] In mortality assessments of diabetes patients, coronary heart disease had almost three times higher risk of death in individuals with diabetes; other CVDs such as stroke and heart failure were not as strongly linked to diabetes, but were also significantly linked to higher mortality.[1,6] The most common trigger for cardiovascular events is the rupture of an atherosclerotic plaque and subsequent platelet aggregation. Thus, early detection of atherosclerosis can be helpful in screening for CVD.[7] It had been reported that arterial stiffness, which reflects vascular and subclinical organ damage and has a strong association with atherosclerosis, is also a surrogate marker for CVD.[8–10] There has been increased interest in measuring aortic stiffness directly, as target organs are more exposed to central hemodynamic changes than peripheral ones.[11] Thus, carotid-femoral pulse wave velocity (cfPWV), a predictor that is strongly correlated with future all-cause and CVD mortality and is independent of classic cardiovascular risk factors, has become the gold standard for noninvasive measurement of aortic stiffness.[9,12]

Adipocyte fatty acid binding protein (A-FABP), also termed FABP-4, is a fat-derived circulating protein and one of the most abundant proteins in mature adipocytes. It affects lipolysis, lipid metabolism, and insulin sensitivity, and promotes atherosclerosis, insulin resistance, and hypertriacylglycerolaemia.[13] Elevated circulating A-FABP induces endothelial dysfunction and stimulates the occurrence of further cardiometabolic syndrome.[13] Accumulating evidence suggests that A-FABP is positively associated with adiposo-

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pathy-induced atherosclerosis, metabolic syndrome (MetS), diabetes, and CVD.[14,15] Therefore, A-FABP is one of the most promising biomarkers and potential therapeutic targets for MetS and CVD.[13] Our previous study demonstrated that increased serum A-FABP levels are a significant risk factor in developing aortic stiffness in the geriatric population.[14] As there is a strong correlation between DM, CVD, and aortic stiffness, we wanted to determine whether A-FABP is an independent predictor of aortic stiffness in geriatric T2DM patients.

2. Materials and methods

2.1. Participants

Between November 2014 and March 2015, 120 T2DM patients over 65 years of age were recruited from the endocrine outpatient department in a medical center in Hualien, Taiwan. The Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation approved this study. All participants provided informed consent before any study-related procedures were performed (IRB103-136-B). DM was diagnosed if their fasting plasma glucose level was $\geq$ 126 mg/dl or they used oral hypoglycemic medications or insulin.[16]

Blood pressure (BP) was measured by trained staff using standard mercury sphygmomanometers with appropriate cuff sizes after the participant has been seated for at least 10 min in the morning. Systolic and diastolic BP readings were taken three times at 5-min intervals and averaged for analysis. Hypertension was diagnosed with an average BP $\geq$ 140/90 mmHg or if a patient had been taking antihypertensive medications in the previous two weeks. Subjects were excluded if they had type 1 DM, pulmonary edema, malignancy, an acute infection at the time of blood sampling, or declined to provide informed consent.

2.2. Anthropometric analysis

In light clothing and without shoes, each participant's body weight and height were measured to the nearest 0.5 kg and 0.5 cm, respectively. With hands on the hips, waist circumference (WC) was measured at the midpoint between the lowest ribs and the iliac crest. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Body fat mass was measured by bioimpedance at the bedside using the standard tetrapolar whole-body (hand-foot) technique using a single-frequency (50-kHz) analyzer (Biodynamic-450, Biodynamics Corporation, Seattle, USA) and analyzed using specific formulas supplied by the manufacturer.[14,17,18] The same operator performed all measurements.

2.3. Biochemical investigations

Approximately 5 ml of overnight fasting blood samples were immediately centrifuged at 3000 $\times$ *g* for 10 min. Serum concentrations of glucose, glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), creatinine, total cholesterol (TCH), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and urine protein-to-creatinine ratio (UPCR) using random spot urine testing were measured using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany).[14,18,20,21] The estimated glomerular filtrationrate (eGFR) was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Serum levels of A-FABP (EIA; SPI-BIO, Montigny le Bretonneux, France) were assessed using a commercially available enzyme immunoassay (EIA).[14,17,18]

2.4. Carotid-femoral pulse wave velocity (cfPWV) measurements

We use applanation tonometry (SphygmoCor system, AtCor Medical, Australia) to measure cfPWV by transcutaneously recording the pressure pulse waveform in the underlying artery, as previously described.[14,18] Measurements were taken in the morning in a temperature-controlled room, with patients in the supine position following a minimum of 10 minutes of rest. ECG signals were recorded simultaneously to provide an R-timing reference. Pulse wave recordings were performed consecutively at two superficial artery sites (carotid-femoral segment), with the distance obtained by subtracting the distance from the carotid measurement site to the sternal notch and from the sternal notch to the femoral measurement site. An integral software was used to process each set of pulse wave and ECG data and calculate the mean time difference between the *R*-wave and the pulse wave on a beat-to-beat basis, with an average of 10 consecutive cardiac cycles. The cfPWV was calculated using the distance and the mean time difference between the two recorded points. Quality indices, included in the software, were set to ensure uniformity of the data. According to the 2013 European Society of Hypertension and the European Society of Cardiology guidelines, we defined aortic stiffness as having cfPWV values > 10 m/s, while values $\leq$ 10 m/s were included in the control group.[19]

2.5. Statistical analysis

The distribution pattern of the data was tested using the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean $\pm$ standard deviation, and comparisons between participants were performed using the Student's independent t-test (two-tailed). Non-normally distributed data are expressed as medians and interquartile ranges, and comparisons between participants were performed via the Mann-Whitney U test (age, fasting glucose, HbA1c, BUN, creatinine, TG, UPCR, and A-FABP). Data that includes categorical data were analyzed by the chi-square test. Variables that were significantly associated with aortic stiffness in geriatric persons with T2DM were tested for independence using multivariate logistic regression analysis. Because the age, fasting glucose, BUN, creatinine, TG, UPCR, and A-FABP levels were not normally distributed, they underwent base 10 logarithmic transformations to achieve normality. Variables that were significantly associated with cfPWV values in geriatric persons with T2DM were tested for independence in linear regression analyses and then multivariate forward stepwise regression analyses. The analyses were performed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

3. Results

Demographic, clinical, biochemical, and medication data for the 120 geriatric persons with T2DM are presented in Table 1. In total, 57 (47.5%) participants were included in the aortic stiffness group and the remaider were included in the control group. Geriatric persons with T2DM in the aortic stiffness group had higher SBP (p = 0.031) and serum A-FABP levels (p < 0.001) than those in the control group. There were no statistically significant differences in sex, hypertension, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, statins, fibrate, metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitor, peroxisome proliferator-activated receptor gamma agonist, or insulin between the two groups.

The association of aortic stiffness with serum A-FABP levels, as determined by logistic regression analyses, is presented in Table 2. Serum A-FABP levels associated with aortic stiffness found that an increase in A-FABP of 1 ng/ml (odds ratio (OR): 1.064, 95% confidence interval (CI): 1.027–1.102, p = 0.001) increased the risk of aortic stiffness in geriatric persons with T2DM by 6.4% using unadjusted logistic regression analysis. Adjusting for age and gender gave a 7.1% increase in the risk of aortic stiffness (OR: 1.071, 95% CI: 1.031–1.114, p < 0.001) for every increase of 1 ng/ml A-FABP using multivariate logistic regression analysis (Model 1). An increased risk of 7.9% for aortic stiffness (OR: 1.079, 95% CI: 1.034–1.126, p < 0.001) was observed for every 1 ng/ml increase in A-FABP by multivariate logistic regression analysis with Model 1 plus BUN, creatinine, and eGFR levels (Model 2). We observed an increased risk of 7.8% for aortic stiffness (OR: 1.078, 95% CI: 1.032–1.126, p = 0.001) for every 1 ng/ml increase in A-FABP using multivariate logistic regression analysis using Model 2 while including SBP, DBP, and hypertension (Model 3). In geriatric persons with T2DM, all of these analyses confirmed that serum A-FABP levels are positively associated with aortic stiffness.

Subgroup analysis of cfPWV values in geriatric persons with T2DM by univariate and multivariate linear analyses is presented in Table 3. WC (r = 0.245, p = 0.007), body fat mass (r = 0.185, p = 0.043), SBP (r = 0.227, p = 0.013), logarithmically transformed TG

Table 1
Clinical variables of the 120 geriatric diabetic patients with or without aortic stiffness.

Characteristics	All patients (n = 120)	Control group (n = 63)	Aortic stiffness group (n = 57)	p value
Age (years)	71.50 (68.00–77.00)	70.00 (67.00–76.00)	73.00 (68.00–78.00)	0.094
Height (cm)	159.53 ± 8.99	159.53 ± 8.73	159.53 ± 9.34	0.997
Body weight (kg)	69.29 ± 13.06	68.79 ± 13.33	69.85 ± 12.85	0.660
Body mass index (kg/m^2)	27.09 ± 3.75	26.91 ± 4.08	27.29 ± 3.39	0.580
Waist circumference (cm)	91.81 ± 10.17	90.18 ± 10.91	93.61 ± 9.04	0.065
Body fat mass (%)	31.04 ± 6.97	29.98 ± 7.15	32.22 ± 6.63	0.079
cfPWV (m/s)	10.59 ± 3.34	8.26 ± 1.35	13.17 ± 2.97	< 0.001*
SBP (mmHg)	146.98 ± 19.52	143.33 ± 18.62	151.00 ± 19.87	0.031*
DBP (mmHg)	80.43 ± 10.56	79.68 ± 10.22	81.26 ± 10.96	0.415
Total cholesterol (mg/dl)	151.01 ± 30.80	148.95 ± 28.63	153.28 ± 33.14	0.444
Triglyceride (mg/dl)	111.00 (85.75–157.50)	109.00 (80.00–148.00)	114.00 (94.00–162.50)	0.267
LDL-C (mg/dl)	87.60 ± 26.88	84.71 ± 25.39	90.16 ± 28.40	0.270
Fasting glucose (mg/dl)	130.00 (112.25–159.00)	130.00 (110.00–155.00)	131.00 (114.50–163.00)	0.644
Glycated hemoglobin (%)	7.10 (6.50–8.28)	7.00 (6.50–7.90)	7.20 (6.55–8.30)	0.396
Blood urea nitrogen (mg/dl)	22.00 (16.25–31.00)	24.00 (16.00–30.00)	21.00 (16.50–35.50)	0.846
Creatinine (mg/dl)	1.15 (0.80–1.80)	1.10 (0.80–1.70)	1.20 (0.80–1.90)	0.985
eGFR (ml/min)	60.60 ± 30.38	60.38 ± 27.38	60.83 ± 33.62	0.936
UPCR (mg/g)	97.24 (0.00–299.73)	104.69 (33.10–230.12)	95.64 (0.00–416.74)	0.738
A-FABP (ng/ml)	14.15 (7.66–25.72)	9.85 (5.98–18.20)	19.49 (10.70–28.33)	< 0.001*
Female, n (%)	50 (41.7)	24 (38.1)	26 (45.6)	0.404
Hypertension, n (%)	85 (70.8)	46 (73.0)	39 (68.4)	0.580
ACE inhibitor use, n (%)	2 (1.7)	0 (0)	2 (3.5)	0.134
ARB use, n (%)	55 (45.8)	27 (42.9)	28 (49.1)	0.492
β-blocker use, n (%)	33 (27.5)	15 (23.8)	18 (31.6)	0.341
CCB use, n (%)	50 (41.7)	26 (41.3)	24 (42.1)	0.926
Statin use, n (%)	56 (46.7)	31 (49.2)	25 (43.9)	0.558
Fibrate use, n (%)	9 (7.5)	5 (7.9)	4 (7.0)	0.849
Metformin use, n (%)	53 (44.2)	26 (41.3)	27 (47.4)	0.502
Sulfonylureas use, n (%)	69 (57.5)	39 (61.9)	30 (52.6)	0.305
DDP-4 inhibitor use, n (%)	58 (48.3)	34 (54.0)	24 (42.1)	0.194
PPAR-γ agonist, n (%)	7 (5.8)	5 (7.9)	2 (3.5)	0.301
Insulin use, n (%)	31 (25.8)	19 (30.2)	12 (21.1)	0.255

Values for continuous variables are given as mean ± standard deviation and tested by Student's t-test; variables not normally distributed are given as median and interquartile range and tested by Mann-Whitney U test; values are presented as number (%) and analysis was done using the chi-square test.
AS, arterial stiffness; cfPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio; A-FABP, adipocyte fatty acid binding protein; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DDP-4, dipeptidyl peptidase 4; PPAR-γ, peroxisome proliferator-activated receptor gamma.
* p < 0.05 was considered statistically significant.

Table 2
Odds ratio for aortic stiffness by multivariate logistic regression analysis of adipocyte fatty acid binding protein levels among the 120 geriatric diabetic patients.

A-FABP (ng/ml)	Unadjusted		Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Per 1 ng/ml increase	1.064 (1.027–1.102)	0.001*	1.071 (1.031–1.114)	< 0.001*	1.079 (1.034–1.126)	< 0.001*	1.078 (1.032–1.126)	0.001*

Model 1 is adjusted for age and gender. Model 2 is adjusted for the Model 1 variables and for blood urea nitrogen, creatinine, estimated glomerular filatration, urine protein-to-creatinine ratio. Model 3 is adjusted for the Model 2 variables and systolic blood pressure, diastolic blood pressure and hypertension.
A-FABP, adipocyte fatty acid binding protein; OR, odds ratio; CI, confidence interval.
* p < 0.05 by multivariate logistic regression analysis.

Table 3
Correlation between carotid-femoral pulse wave velocity levels and clinical variables among the 120 geriatric diabetic patients.

Variables	Carotid-femoral pulse wave velocity (m/s)				
	Simple linear regression		Multivariable linear regression		
	r	p value	Beta	Adjusted R^2 change	p value
Female	0.102	0.267	-	-	-
Hypertension	0.021	0.820	-	-	-
Log-age (years)	0.141	0.125	-	-	-
Height (cm)	0.070	0.449	-	-	-
Body weight (kg)	0.083	0.369	-	-	-
Body mass index (kg/m^2)	0.060	0.516	-	-	-
Waist circumference (cm)	0.245	0.007*	0.188	0.052	0.035*
Body fat mass (%)	0.185	0.043*	-	-	-
SBP (mmHg)	0.227	0.013*	0.188	0.027	0.034*
DBP (mmHg)	0.150	0.103	-	-	-
Total cholesterol (mg/dl)	0.051	0.579	-	-	-
Log-Triglyceride (mg/dl)	0.212	0.020*			
LDL-C (mg/dl)	0.032	0.732	-	-	-
Log-glucose (mg/dl)	0.019	0.836	-	-	-
Log-HbA1c (%)	0.084	0.362	-	-	-
Log-BUN (mg/dl)	0.060	0.517	-	-	-
Log-creatinine (mg/dl)	0.130	0.156	-	-	-
eGFR (mL/min)	-0.143	0.120	-	-	-
Log-UPCR (mg/g)	0.140	0.126	-	-	-
Log-A-FABP (ng/ml)	0.240	0.008*	0.217	0.040	0.013*

Data of age, triglyceride, glucose, HbA1c, BUN, creatinine, UPCR, and A-FABP levels showed skewed distribution and therefore were log-transformed before analysis.
Analysis of data was done using the univariate linear regression analyses or multivariate stepwise linear regression analysis (adapted factors were waist circumference, body fat mass, SBP, log-Triglyceride, and log-A-FABP).
SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio; A-FABP, adipocyte fatty acid binding protein.
* $p < 0.05$ was considered statistically significant.

(log-TG, r = 0.212, p = 0.020), and log-A-FABP (r = 0.240, p = 0.008) positively correlated with cfPWV values in geriatric persons with T2DM. Multivariate forward stepwise linear regression analysis of the variables significantly associated with cfPWV values revealed that WC (β = 0.188, adjusted R^2 change = 0.052, p = 0.035), SBP (β = 0.188, adjusted R^2 change = 0.027, p = 0.034), and log-A-FABP (β = 0.217, adjusted R^2 change = 0.040, p = 0.013) were independent predictors of cfPWV values in geriatric persons with T2DM.

4. Discussion

The main finding of our study is that serum A-FABP level is associated with aortic stiffness in geriatric persons with T2DM, with an increased risk of 7.8% for aortic stiffness for every 1 ng/ml increase in A-FABP concentration. Additionally, WC and SBP were also associted with cfPWV values in T2DM geriatric patients.

Arterial stiffness, an independent prognosticate for hypertension and CVD outcomes, is associated with low-grade inflammation and unregulated vascular element change with unorganized elastin fiber and collagen.[10,20] With the aging of populations, there is an increasing prevalence of high arterial stiffness across the globe.[10] Currently, noninvasive cfPWV measurement is widely used to assess the aortic stiffness and is the gold standard indicator of arterial function in the European Society of Hypertension and the European Society of Cardiology guidelines.[19]

The mechanisms that affect arterial stiffness are likely to be multifactorial. While age-related arterial stiffness is well recognized, activation of the renin-angiotensin-aldosterone system (RAAS) system, vascular inflammation, dyslipidemia, and adiposopathy related insulin resistance, and inflammatory adipokines have also been found in conjunction with arterial stiffness.[10,21] The RAAS is activated in conditions of hypertension, as well as in obesity-related diabetes and MetS.[22] Previous studies had revealed that angiotensin II (Ang II) can mediate vascular remodeling in CVD by activating many pro-growth/mitotic pathways, stimulating pro-inflammatory cytokine secretion, inhibiting anti-inflammatory cytokine secretion, and elevating oxidative stress, which taken together can lead to endothelial dysfunction and hypertrophy of vascular smooth muscle.[10,23–25] In addition, Ang II induces vasoconstriction, which may aggravate arterial stiffness, and a recent study revealed that Ang II induced significantly increased vasoconstriction of graft following coronary artery bypass in DM patients versus non-DM patients.[26,27] Moreover, it is well accepted that obesity and obesity-induced insulin resistance are associated with a substantially increased prevalence of vascular fibrosis and stiffness.[28] Dyslipidemia also induces the earliest atherosclerotic lesion and then arterial stiffness.[29] Our study revealed that SBP, WC, body fat mass, and log-TG levels are significant associated with cfPWV values among the geriatric diabetic patients, and SBP accompanied with WC are still significant associated with cfPWV values after multivariate stepwise linear regression analysis.

A-FABP, an intracellular lipid chaperone that regulates intracellular lipid trafficking and responses. It is an adipokine mainly produced by mature adipocytes, though it can also be synthesized in by vascular endothelial cells and macrophages. An epidemiological study revealed that higher serum A-FABP concentration was positively associated with MetS in T2DM patients.[17] A 12-year prospective community-based cohort study demonstrates that circulating A-FABP level predicts the development of CVD after adjustment for traditional risk factors such as BP, BMI, WC, fasting glucose, dyslipidemia, and homeostasis model assessment-insulin resistance.[30] A recent study also confirmed that T2DM women with higher levels of circulating A-FABP at baseline correlated with cardiovascular mortality.[31] Previous studies determined that serum A-FABP levels are an essential risk factor in developing aortic stiffness in the geriatric

population and hypertension patients with MetS.[14,18] As a pro-inflammatory adipokine, A-FABP may contribute to the pathogenesis of atherosclerosis and arterial stiffness by different mechanisms.[13] A-FABP produced by adipocytes regulates transportation of non-esterified fatty acids (NEFAs) and pro-adipogenic peroxisome proliferator-activated receptor γ (PPARγ) agonists through a ligand/ligand delivery mechanism, and interacts with proteins that influence lipid metabolism and insulin sensitivity, leading to insulin resistance, NEFAs release, and pro-inflammatory gene expression.[13,32] Also, the aggravaton of atherosclerosis by A-FABP is related to its action in macrophages, rather than its action in adipocytes.[13,33] A-FABP overexpression in macrophages triggered by saturated free fatty acids, oxidized LDL, and Toll-like receptor activators leads to TG and cholesterol accumulation, induction of foamy cell development, and stimulation of macrophage infiltration and accumulation into adipose tissue.[13] A human A-FABP functionally genetic variant (T-87C polymorphism) presents as reduced adipocyte A-FABP expression and lowered serum TG levels, has lower the risk of CVD and T2DM in a population study.[34] Treatment with BMS309403, an A-FABP inhibitor, significantly decreases macrophage production of pro-inflammatory cytokines and alleviates the progression of atherosclerosis.[35] These findings indicate that A-FABP affects atherosclerosis, insulin resistance, and hypertriacylglycerolaemia, which all aggravate the progression of aortic stiffness.[13,36] This study also noted that serum log-A-FABP level is positively correlated with cfPWV values in geriatric persons with T2DM. After adjusting the confounding factors, the multivariable logistic regression analysis revealed that an increased serum A-FABP level was an independent predictor of aortic stiffness in geriatric persons with T2DM.

Our study had some limitations. First, this cross-sectional study was performed in a single center with limited sample size, and without accounting for some lifestyle habits that could influence the occurrence of aortic stiffness, such as smoking, alcohol consumption, and physical activity.[37] In addition, the possibility of bias cannot be excluded and the cohort may be hard to represent the whole population in Taiwan, so further longitudinal studies are needed before a cause-effect relationship can be established. Second, pharmacological interventions may influence serum atherosclerotic and inflammatory status in humans.[38] In this study, the results did not show that treatment with statins, fibrates, or other antidiabetic drugs had an influence on aortic stiffness in the diabetic geriatric patients studied. However, further studies are required to clarify the relationship between the aforementioned medications and aortic stiffness in T2DM patients.

In summary, serum A-FABP level is positively associated with cfPWV values in geriatric persons with T2DM; moreover, high serum A-FABP levels are positively associated with aortic AS among these patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Baena-Díez JM, Peñafiel J, Subirana I, et al. Risk of cause-specific death in individuals with diabetes: a competing risks analysis. *Diabetes Care.* 2016;39:1987–1995.
2. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* 2018;138:271–281.
3. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. *Diabetes Care.* 2018; 41(Suppl 1):S13–S27.
4. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321:405–412.
5. Einarson TR, Acs A, Ludwig C. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. 2018;17:83.
6. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375:2215–2222.
7. Stirban AO, Tschoepe D. Cardiovascular complications in diabetes: targets and interventions. *Diabetes Care.* 2008;31 Suppl 2:S215–S221.
8. van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke.* 2001;32:454–460.
9. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;55:1318–1327.
10. Dumor K, Shoemaker-Moyle M, Nistala R, et al. Arterial stiffness in hypertension: an update. *Curr Hypertens Rep.* 2018;20:72.
11. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension.* 2007;50:197–203.
12. David M, Malti O, AlGhatrif M, et al. Pulse wave velocity testing in the Baltimore longitudinal study of aging. *J Vis Exp.* 2014;84:e50817.
13. Kralisch S, Fasshauer M. Adipocyte fatty acid binding protein: a novel adipokine involved in the pathogenesis of metabolic and vascular disease? *Diabetologia.* 2013;56:10–21.
14. Tsai JP, Wang JH, Lee CJ, et al. Positive correlation of serum adipocyte fatty acid binding protein levels with carotid-femoral pulse wave velocity in geriatric population. *BMC Geriatr.* 2015;15:88.
15. Ebert T, Gebhardt C, Scholz M, et al. Relationship between 12 adipocytokines and distinct components of the metabolic syndrome. *J Clin Endocrinol Metab.* 2018;103:1015–1023.
16. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15:539–553.
17. Li JC, Wu DA, Hou JS, et al. High serum adipocyte fatty acid binding protein is associated with metabolic syndrome in patients with type 2 diabetes. *J Diabetes Res.* 2016;2016:8380279.
18. Chen MC, Hsu BG, Lee CJ, et al. High serum adipocyte fatty acid binding protein level as a potential biomarker of aortic arterial stiffness in hypertensive patients with metabolic syndrome. *Clin Chim Acta.* 2017;473: 166–172.
19. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013; 31:1281–1357.
20. Safar ME. Arterial stiffness as a risk factor for clinical hypertension. *Nat Rev Cardiol.* 2018;15:97–105.
21. Lyle AN, Raaz U. Killing me unsoftly: Causes and mechanisms of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2017;37:e1–e11.
22. Wu LE, Samocha-Bonet D, Whitworth PT, et al. Identification of fatty acid binding protein 4 as an adipokine that regulates insulin secretion during obesity. *Mol Metab.* 2014;3:465–473.
23. Aragones G, Ferré R, Lázaro I, et al. Fatty acid-binding protein 4 is associated with endothelial dysfunction in patients with type 2 diabetes. *Atherosclerosis.* 2010;213:329–331.
24. Cabré A, Lázaro I, Girona J, et al. Fatty acid binding protein 4 is increased in metabolic syndrome and with thiazolidinedione treatment in diabetic patients. *Atherosclerosis.* 2007;195:e150–e158.
25. Park SE, Rhee EJ, Lee WY, et al. The role of serum adipocyte fatty acid-binding protein on the development of metabolic syndrome is independent of pro-inflammatory cytokines. *Nutr Metab Cardiovasc Dis.* 2012;

22:525–532.
26. Nichols WW, Epstein BJ. Actions of selected cardiovascular hormones on arterial stiffness and wave reflections. *Curr Pharm Des.* 2009;15:304–320.
27. Yokota A, Gamoh S, Tanaka-Totoribe N, et al. Angiotensin II, as well as 5-hydroxytriptamine, is a potent vasospasm inducer of saphenous vein graft for coronary artery bypass grafting in patients with diabetes mellitus. *Biochem Biophys Rep.* 2016;6:82–87.
28. Jia G, Aroor AR, DeMarco VG, et al. Vascular stiffness in insulin resistance and obesity. *Front Physiol.* 2015;6:231.
29. Pires A, Sena C, Seiça R. Dyslipidemia and cardiovascular changes in children. *Curr Opin Cardiol.* 2016;31:95–100.
30. Chow WS, Tso AW, Xu A, et al. Elevated circulating adipocyte-fatty acid binding protein levels predict incident cardiovascular events in a community-based cohort: a 12-year prospective study. *J Am Heart Assoc.* 2013;2:e004176.
31. Lee CH, Cheung CYY, Woo YC, et al. Circulating adipocyte fatty acid-binding protein concentrations predict multiple mortality outcomes among men and women with diabetes. *Clin Chem.* 2018;64:1496–1504.
32. Hertzel AV, Bernlohr DA. The mammalian fatty acid-binding protein multigene family: molecular and genetic insights into function. *Trends Endocrinol Metab.* 2000;11:175–180.
33. Furuhashi M, Saitoh S, Shimamoto K, et al. Fatty Acid-binding protein 4 (FABP4): Pathophysiological insights and potent clinical biomarker of metabolic and cardiovascular diseases. *Clin Med Insights Cardiol.* 2015; 8(Suppl 3):23–33.
34. Tuncman G, Erbay E, Hom X, et al. A genetic variant at the fatty acid-binding protein aP2 locus reduces the risk for hypertriglyceridemia, type 2 diabetes, and cardiovascular disease. *Proc Natl Acad Sci USA.* 2006;103: 6970–6975.
35. Furuhashi M, Tuncman G, Görgün CZ, et al. Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. *Nature.* 2007;447:959–965.
36. El Husseny MW, Mamdouh M, Shaban S, et al. Adipokines: Potential therapeutic targets for vascular dysfunction in type II diabetes mellitus and obesity. *J Diabetes Res.* 2017;2017:8095926.
37. Camplain R, Meyer ML, Tanaka H, et al. Smoking behaviors and arterial stiffness measured by pulse wave velocity in older adults: the atherosclerosis risk in communities (ARIC) study. *Am J Hypertens.* 2016;29: 1268–1275.
38. Upala S, Wirunsawanya K, Jaruvongvanich V, et al. Effects of statin therapy on arterial stiffness: A systematic review and meta-analysis of randomized controlled trial. *Int J Cardiol.* 2017;227:338–341.