ORIGINAL RESEARCH

Lower Plasma Albumin, Higher White Blood Cell Count and High-Sensitivity C-Reactive Protein are Associated with Femoral Artery Intima-Media Thickness Among Newly Diagnosed Patients with Type 2 Diabetes Mellitus

Nga Phi Thi Nguyen[1,2],*, Thuc Luong Cong[3,4],*, Thi Thanh Hoa Tran [5], Binh Nhu Do[6], Son Tien Nguyen [1,2], Binh Thanh Vu [7],*, Lan Ho Thi Nguyen[8], Manh Van Ngo[9], Hoa Trung Dinh [10], Hoang Duong Huy [11], Nghia Xuan Vu [12], Kien Nguyen Trung [13], Duong Ngoc Vu[14], Nghia The Pham[14], Tuan Dinh Le [2,15],*

[1]Department of Endocrinology, Military Hospital 103, Hanoi, Vietnam; [2]Department of Rheumatology and Endocrinology, Vietnam Military Medical University, Hanoi, Vietnam; [3]Cardiovascular Center, Military Hospital 103, Hanoi, Vietnam; [4]Department of Cardiology, Vietnam Military Medical University, Hanoi, Vietnam; [5]Emergency Resuscitation Department, National Hospital of Endocrinology, Hanoi, Vietnam; [6]Division of Military Science, Military Hospital 103, Vietnam Military Medical University, Hanoi, Vietnam; [7]Department of Internal Medicine, Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam; [8]Department of General Internal Medicine, National Hospital of Endocrinology, Hanoi, Vietnam; [9]Postgraduate Training Management Department, Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam; [10]Department of Requested Treatment, National Hospital of Endocrinology, Hanoi, Vietnam; [11]Department of Neurology, Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam; [12]Department of Blood Transfusion, 108 Military Central Hospital, Hanoi, Vietnam; [13]Department of Science Management, Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam; [14]Department of Imaging Diagnosis, Hanoi Medical University, Hanoi, Vietnam; [15]Center of Emergency, Critical Care Medicine and Clinical Toxicology, Military Hospital 103, Vietnam Military Medical University, Hanoi, Vietnam

*These authors contributed equally to this work

Correspondence: Tuan Dinh Le, Center of Emergency, Critical Care Medicine and Clinical Toxicology, Military Hospital 103, Vietnam Military Medical University, 261 Phung Hung Street, Phuc La Ward, Ha Dong District, Hanoi, Vietnam, Tel +84 388166078, Email letuan985@gmail.com; Binh Thanh Vu, Department of Internal Medicine, Thai Binh University of Medicine and Pharmacy, 373 Ly Bon Street, Ky Ba Ward, Thai Binh, Vietnam, Tel +84 334588298, Email binhvt@tbump.edu.vn

Introduction: Low albumin levels, high levels of high-sensitivity C-reactive protein (hs-CRP), and high white blood cell count were risk factors for changes in arterial intima-media thickness (IMT). Femoral artery IMT damages were one of the common peripheral artery type 2 diabetes. This study was conducted to determine the association between femoral artery IMT and plasma albumin, hs-CRP levels, and white blood cell count in newly diagnosed patients with type 2 diabetes mellitus (nT2D).

Materials and Methods: From January 2015 to May 2020, 306 patients with nT2D were recruited for this cross-sectional descriptive study at Vietnam's National Endocrinology Hospital. We measured IMT by Doppler ultrasound.

Results: There was a statistically significant difference in albumin, hs-CRP levels, hs-CRP-to-albumin ratio, and white blood cell counts between three different IMT groups namely normal IMT, thick IMT, and atherosclerosis ($p = 0.003$, $p = 0.001$, $p = 0.001$ and $p = 0.049$, respectively). In the multivariate linear regression analysis, white blood cell count, and hs-CRP levels showed a significantly positive correlation to IMT (standardized B and p of 0.17, 0.015 and 0.163, 0.024, respectively), but albumin levels were a significantly negative correlation to IMT (standardized B = –0.151, $p = 0.029$). The multivariate logistic regression analysis showed that albumin (OR = 0.79, 95% CI 0.65–0.90, $p = 0.018$), hs-CRP (OR = 1.09, 95% CI 1.01–1.18, $p = 0.026$), and white blood cell count (OR = 1.36, 95% CI 1.03–1.81, $p = 0.033$) had correlation to atherosclerosis of femoral artery.

Conclusion: Reduced plasma albumin, elevated hs-CRP, and white blood cell count associated with IMT increased the odds for atherosclerosis of femoral artery among nT2D.

Introduction

The number of diabetes has been rising rapidly in the world. As of 2019, 79% of adults with diabetes were living in low- and middle-income countries.[1,2] Macro- and micro-vascular complications due to prediabetes or diabetes increase the burden on the healthcare system and society, also reduce the patient's quality of life in these countries.[3–6] Peripheral arterial disease is a major macrovascular complication of type 2 diabetes that can lead to limb amputation and enhance the risk of morbidity and mortality in diabetic patients.[7–9]

Common femoral arterial damages are one of the peripheral arterial diseases, with endothelium dysfunction, thick intima-media, and atherosclerosis.[7] Recently, researchers have turned their focus on the potential role of the femoral arterial IMT in evaluating cardiovascular complications in diabetic patients.[10–12] It is indisputable that cardiovascular risk factors (for example, age, duration of type 2 diabetes, smoking, hypertension, hyperglycemia, dyslipidemia, overweight, and obesity) in diabetic patients promote endothelium dysfunction and atherosclerosis of femoral arteries.[7,11] Diabetes enhances the risk of inflammation via increases in hs-CRP, interleukin (such as interleukin-4,6,8,17), tumor necrosis factor-alpha, platelet adhesion and aggregation, and coagulation disorders, which contributes to developing endothelium dysfunction.[7,13,14] Recent studies have demonstrated hypoalbuminemia and an increase in inflammatory factors such as hs-CRP and white blood cell count are the main factors for endothelium dysfunction and atherosclerosis in diabetic patients.[15–18] Plasma albumin protects against endothelial dysfunction via immunomodulatory and antioxidant function.[19] High-sensitive CRP and white blood cell count have contradictory pro-angiogenic, anti-angiogenic effects, and inhibit nitric oxide synthase determining tissue remodeling in the atherosclerotic plaque.[20,21] Besides, the hs-CRP-to-albumin ratio is a new marker to predict inflammatory events, with increased hs-CRP-to-albumin ratio playing a role in the pathogenesis of coronary slow flow, coronary artery disease.[22,23]

Whilst there are many patients with clinically femoral arterial atherosclerosis, there are few studies on femoral arterial IMT among patients with type 2 diabetes mellitus. Vietnam is one of the developing countries, the number of nT2D and vascular complications has increased rapidly. Nevertheless, there is a lack of studies on the role of plasma albumin, hs-CRP levels, and white blood cell count in femoral artery lesions. This study was conducted to investigate the association between femoral arterial IMT and plasma albumin, hs-CRP, and white blood cell count in nT2D.

Materials and Methods
Study Population and Design

A cross-sectional descriptive study was conducted on 306 patients with nT2D in the National Endocrinology Hospital (Hanoi, Vietnam) from January 2015 to December 2020. All participants provided written informed consents. The diagnosis of type 2 diabetes mellitus was based on the American Diabetes Association guideline (2019)[24] for the first time on examination day to minimize other treatment-related factors such as acarbose, miglitol, metformin, insulin therapy. Exclusion criteria included patients that suffered from severe chronic liver failure (cirrhosis or acute liver failure), heart failure (with a mid-range and reduced ejection fraction [EF] <50%), or kidney failure (with estimated glomerular filtration rate estimation [eGFR] <45 [mL/min]), hemodynamic diseases (aplastic anemia, moderate-to-severe anemia, and hemolytic anemia), systemic diseases (systemic lupus erythematosus, and peripheral arterial occlusive diseases), infections, and critical diabetic conditions (hyperosmolarity, diabetic ketoacidosis, and hypogly-cemia), and who were undergoing anticoagulant treatment from the study (sintrom, aspirin, clopidogrel, and heparin).

The sample size (n) of 306 patients with nT2DM was calculated based on Cochran's formula used for qualitative analysis in descriptive and analytical research as follows n = $[Z^2_{(1-\alpha/2)} \times p(1 - p)]/\Delta^2$, where p = 0.228 is the rate of increased aortic-IMT in adult diabetes mellitus patients,[25] $Z^2_{(1-\alpha/2)}$ = 1.96 is the value corresponding to α = 0.05 and Δ is the desired deviation between the rate obtained from our study sample and p of 0.228 of the previous study population. In

our study, $\Delta = 0.05$. In order to avoid potential loss of data, we decided to include 10% more patients in our study population.

Clinical and Biochemical Assessments

All patients were questioned about their comorbid conditions and medication consumption histories. Anthropometric measurements and clinical examination were collected, with drinking, smoking history, age, gender, height, weight, waist and hip circumference, waist-to-hip ratio (WHR), body mass index (BMI), pulses, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Blood samples were taken on the morning of clinical examination day after a fast of at least 8 hours. Blood lipid profiles (total cholesterol, high-density lipoprotein [HDL-C], and triglyceride), aspartate transferase (AST), alanine transferase (ALT), creatinine, electrolytes, albumin, and hs-CRP were measured by the enzyme colorimetric method (Beckman AU680, USA). Low-density lipoprotein (LDL-C) was calculated by Friedewald formula (all variables in mmol/L) as follow:

$$LDL - C = 0.026 \times \left(38.67 \times [\text{Total cholesterol}] - 38.67 \times [HDL - C] - 88.57 \times \frac{\text{Triglyceride}}{5} \right)$$

Chemiluminescent enzyme immunoassays for the measurement of C-peptide and insulin (COBAS E411, USA). HbA1c was measured by high-performance liquid chromatography (Adams A1C, Japan), Quantification of fasting glucagon-like peptide-1 (fGLP-1) levels by enzyme-linked immunosorbent assay (Human ELISA GLP-1 kits, IBL, Japan, #27784). We used the hexokinase methods (Beckman AU680, USA) to measure fasting plasma glucose (FPG) and two-hour postprandial glucose (2h-PPG) and enzymatic turbidimeter autoanalyzer (Beckman AU680, USA) to measure urine albumin levels in a 24-hour urine sample (24hUA). The white blood cell was counted using K-4500, Japan. Evaluation of eGFR by Cockcroft-Gault's formula from serum creatinine (S_{cr}) in adult males (15% less in females)[26] as follow:

$$eGFR = \frac{(140 - age[\text{years}]) \times (\text{body weight}[\text{kg}])}{S_{cr}(\mu mol/L)}$$

Bilateral Femoral Arteries Findings by Ultrasonography

Patients were guided to lay in the supine position with flexible lower extremities. Under the standardized protocol for ultrasound in Vietnam, experienced ultrasound practitioners investigated femoral arteries from the inguinal ligament position downwardly to common femoral arteries to the bifurcation of the femoral artery into the subsartorial artery and the deep femoral artery by Philip HD 11 XE Color Doppler apparatus using a linear transducer (frequency of 7.5 MHz). Colored Doppler and continuous Doppler modes were employed to investigate the morphology and functions of arteries. The position for evaluating IMT (mm) was at the distal walls of femoral arteries which were 2 cm from the bifurcation of the femoral artery into subsartorial artery and deep femoral artery.[27] Following Pignoli's method,[28] the IMT measurements were performed at both femoral arteries and the highest IMT was reported as an IMT variable for each patient, and then classified into 3 categories, namely normal IMT (less than 1 mm), thick IMT ($1 \leq IMT < 1.5$ mm), and atherosclerosis (IMT ≥ 1.5 mm).[29,30]

Ethical Statement

All participants provided written informed consents and agreed to join our study; and the protocol was approved by the Ethical Review Committee of Vietnam Military Medical University, Vietnam (Reference No 168/2014/IRB-VMMU). The study was also conducted using good clinical practice following the Declaration of Helsinki.

Statistical Analysis

Data were expressed as mean ± standard deviation or median (interquartile range, Q1-Q3). Differences between groups were examined with either Student's t-test or Mann–Whitney test. Correlations between plasma albumin, hs-CRP levels, white blood cell count, and other variables were evaluated with Pearson's and Spearman correlation analysis, respectively. The Chi-square test

of association is used to discover if there is a relationship between two categorical variables. Kruskal–Wallis H-tests with Dunn's pairwise post hoc tests were used to analyze the differences in plasma albumin, hs-CRP levels, white blood cell count between groups of IMT. Multivariate linear regression was employed to analyze the effects of plasma albumin, hs-CRP levels, white blood cell count, and other related factors and IMT. The VIF value < 10 was defined as no collinear for each variable in the multivariate regression. Multivariate logistic regression analysis was used to analyze the effects of related factors and abnormal IMT and atherosclerosis of the femoral artery. Due to the fact that age, BMI, blood pressure, FPG, lipid profiles, eGFR, urine protein, C-peptide, red blood cells, and potassium related to the development of abnormalities in IMT, we considered these variables as confounders and to be adjusted for multivariate regression analyses between plasma albumin, hs-CRP levels, white blood cell counts and IMT. A p-value <0.05 was defined as statistically significant. Data were analyzed with the SPSS version 26 (SPSS Inc, Chicago, IL).

Results

Demographic and Biomedical Findings

Age, insulin, C-peptide levels, and platelet count at the time of diagnosing in women patients were higher than those in men. Male patients had higher waist circumference, WHR, femoral arterial IMT, FPG, triglyceride, creatinine, red blood cell count, hemoglobin, 24hUA, and eGFR than female patients. There was no significant difference in hip circumference, BMI, SBP, DBP, 2hr-PPG, HbA1c, fGLP-1, total cholesterol, HDL-C, LDL-C, AST, ALT, hs-CRP, potassium ion, and white blood cell count between male and female patients (Table 1).

A Kruskal–Wallis H-tests showed that there was a significant difference in albumin, hs-CRP levels, hs-CRP-to-albumin ratio, and white blood cell count between the different IMT groups ($\chi^2(2) = 11.703$, p = 0.003; $\chi^2(2) = 13.511$, p = 0.001; $\chi^2(2) = 15.059$, p = 0.001; and $\chi^2(2) = 6.047$, p = 0.049, respectively). Dunn's pairwise tests were carried out for the three pairs of groups (normal, thick IMT and atherosclerosis). Mainly, there was strong evidence (p <0.01, adjusted using Bonferroni corrections) of a difference in albumin and hs-CRP levels between normal IMT and both thick IMT and atherosclerosis group in male patients and in overall ($\chi^2(2) = 7.951$, p = 0.019 and $\chi^2(2) = 10.828$; p = 0.004, respectively) (Table 2).

In the univariate linear regression analysis, femoral arterial IMT significantly correlated to age, waist circumference, WHR, total cholesterol, SBP, DBP, fGLP-1, albumin, hs-CRP, eGFR, and 24hUA. After adjusting for other related factors (namely, waist circumference, WHR, fGLP-1), while age, SBP, hs-CRP, white blood cell count, and potassium ion showed a significantly positive correlation with IMT (Standardized B and p of 0.311, 0.000; 0.275, 0.002; 0.163, 0.024; 0.170, 0.015 and 0.131, 0.042, respectively), albumin levels showed a significant inverse correlation with IMT (standardized B = –0.151 and p = 0.029) (Table 3).

The multivariate logistic regression analysis showed that the following factors correlated to abnormal femoral arterial IMT (including in thick IMT and atherosclerosis) in nT2D: albumin (OR = 0.84, 95% CI 0.71–0.98, p = 0.028), hs-CRP (OR = 1.08, 95% CI 1.01–1.16, p = 0.036), white blood cell count (OR = 1.44, 95% CI 1.13–1.83, p = 0.003), SBP (OR = 1.07, 95% CI 1.02–1.13, p = 0.007), and DBP (OR = 0.92, 95% CI 0.85–0.99, p = 0.036). Albumin, hs-CRP and white blood cell count correlated to atherosclerosis (OR = 0.79, 95% CI 0.65–0.96, p = 0.018; OR = 1.09, 95% CI 1.01–1.18, p = 0.026; OR = 1.36, 95% CI 1.03–1.81, p = 0.033, respectively) (Table 4).

Discussion

The Relation Between Femoral Arterial IMT and Plasma Albumin Levels

This study showed that there was a significant difference in albumin levels among different femoral arterial IMT groups (i.e, normal IMT, thick IMT, and atherosclerosis). In the multivariate linear regression analysis, albumin levels showed an inverse correlation with IMT. The multivariate logistic regression analysis showed that albumin was correlated to thick IMT of the femoral artery in nT2D (OR = 0.84, p = 0.028).

Albumin is the most important plasma protein with many biological functions, including maintenance of colloidal osmotic pressure, binding of endo- and exo-genous substances, and antithrombotic effects.[31] Serum albumin concentrations have also been proved to be inversely associated with various type 2 diabetes risk variables including age, BMI, and

Table 1 The Demographic and Biomedical Characteristics of the Study Population

Variables, Unit	Men	Women	All
Age, years	52.27 ± 10.44[‡]	56.50 ± 9.76[‡]	54.30 ± 10.32
Waist circumference, cm	84.49 ± 7.72[†]	81.94 ± 8.64[†]	83.27 ± 8.26
Hip circumference, cm	92.34 ± 6.63	91.10 ± 7.07	91.80 ± 6.85
BMI, kg/m^2	22.30 (20.70–24.20)	20.60 (20.30–24.20)	22.10 (20.37–24.20)
WHR	0.92 (0.88–0.94) [‡]	0.89 (0.86–0.93) [‡]	0.91 (0.87–0.94)
SBP, mmHg	123.00 (120.00–140.00)	120.00 (120.00–140.00)	120.00 (120.00–140.00)
DBP, mmHg	80.00 (70.00–80.00)	80.00 (70.00–80.00)	80.00 (70.00–80.00)
IMT, mm	0.83 (0.69–1.58)[†]	0.76 (0.65–1.42) [†]	0.82 (0.68–1.45)
FPG, mmol/L	12.00 (8.90–16.20) [†]	10.30 (7.90–14.30) [†]	10.80 (8.30–15.30)
2hr-PPG, mmol/L	15.20 (11.35–18.80)	13.50 (11.00–18.60)	14.60 (11.20–18.68)
HbA1c, %	10.00 (7.70–11.70)	9.40 (7.30–11.40)	9.90 (7.50–11.60)
C-peptide, nmol/L	0.70 (0.45–1.12) [†]	0.81 (0.58–1.20) [†]	0.78 (0.49–1.19)
Insulin, pmol/L	60.93 (34.60–95.30) [†]	78.41 (48.40–118.00) [†]	68.32 (41.32–105.50)
Albumin, g/L	42.00 (39.00–44.00)	41.00 (39.00–44.00)	42.00 (39.00–44.00)
Triglycerides, mmol/L	2.39 (1.47–4.07) [†]	2.02 (1.39–3.24) [†]	2.20 (1.43–3.50)
Total cholesterol, mmol/L	5.56 ± 1.44	5.43 ± 1.43	5.49 ± 1.43
HDL-C, mmol/L	1.17 (1.01–1.43)	1.24 (1.05–1.49)	1.19 (1.03–1.47)
LDL-C, mmol/L	3.38 (2.43–4.18)	3.11 (2.28–4.03)	3.15 (2.44–4.10)
ALT, U/L	33.00 (24.00–52.00)	30.00 (21.00–44.00)	31.00 (23.00–48.25)
AST, U/L	28.00 (11.00–38.00)	28.00 (21.00–36.00)	28.00 (21.00–37.00)
Creatinine, μmol/L	84.00 (75.00–93.00) [‡]	70.00 (63.00–77.00) [‡]	76.00 (67.75–86.25)
eGFR, mL/min	77.78 (65.81–91.86) [‡]	65.03 (56.35–77.40) [‡]	71.22 (59.54–86.29)
fGLP-1, pmol/L	6.27 (4.52–9.44)	6.61 (5.19–8.03)	6.36 (4.92–8.69)
Potassium ion, mmol/L	3.90 (3.67–4.10)	3.80 (3.70–4.00)	3.80 (3.70–4.00)
hsCRP, mg/L	2.21 (1.12–5.26)	2.11 (1.05–4.95)	2.17 (1.10–5.18)
Red blood cell, T/L	5.07 ± 0.65[‡]	4.78 ± 0.43[‡]	4.93 ± 0.57
Hemoglobin, g/L	154.0 (143.0–162.3) [‡]	141.0 (134.0–148.0) [‡]	146.5 (136.8–156.0)
Platelet, G/L	238.0 (204.0–282.0) [‡]	263.0 (237.0–305.0) [‡]	251.5 (219.5–293.3)
White blood cell, G/L	7.88 (6.50–9.51)	7.80 (6.390–9.10)	7.82 (6.45–9.27)
24hUA, mg/L	11.55 (5.20–26.94) [†]	6.33 (4.07–14.77) [†]	8.78 (4.62–22.17)

Notes: Data were illustrated in mean±SD or median (Q1-Q3); [†]P < 0.05; [‡]P < 0.001 (between male and female group).
Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; IMT, intima-media thickness, FPG, fasting plasma glucose, 2hr-PPG, two-hour postprandial glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine transferase; AST, aspartate transferase; eGFR, estimated glomerular filtration rate; fGLP-1, fasting glucagon-like peptide-1; hs-CRP, high-sensitive C reactive protein; 24hUA, 24-h urinary albumin.

insulin resistance.[32–34] Lower serum albumin levels are associated with an increased risk of cardiovascular diseases such as coronary heart disease, ischemic heart disease, cardiovascular mortality, and carotid atherosclerosis.[15,35,36] The antioxidant and anti-inflammatory properties of albumin in the atherogenic process have been hypothesized as possible mechanisms for this inverse association.[37,38]

In this study, although there was no difference in albumin concentration between men and women, albumin concentration was statistically low in males with thickened IMT or atherogenesis of femoral artery, but no difference in females. Moreover, men's IMT was significantly higher than that in women, so the proportion of men with IMT thickness or atherogenesis was higher than women. Besides, reduced plasma albumin is a risk factor for type 2 diabetes,[39] and endothelial dysfunction.[40] At the same time, men have more cardiovascular risk factors and a higher risk of peripheral artery disease than women due to harmful habits, namely smoking, drinking alcohol, metabolic disorders, hypertension, and hypercholesterolemia.[41,42]

Table 2 The Relationship Between Plasma Albumin, Hs-CRP Levels, Hs-CRP-to-Albumin Ratio and White Blood Cell Count and Femoral Arterial Intima-Media Thickness Stratified by Gender and Overall

		Normal IMT	**Thick IMT**	**Atherosclerosis**
Albumin	Mean rank (n) Female Male Overall	79.46 (97) 87.51 (95) 166.41 (192)	62.48 (25) 78.70 (23) 139.74 (48)	64.32 (25) 63.33 (41) 125.94 (66)
	Test Statistics* Female Male Overall	p = 0.093, n = 147 p = 0.019, n = 159 p = 0.003, n = 306		
Hs-CRP	Mean rank (n) Female Male Overall	61.46 (95) 62.83 (84) 123.87 (179)	82.91 (23) 74.71 (21) 158.16 (44)	69.27 (22) 89.35 (37) 161.60 (59)
	Test Statistics* Female Male Overall	p = 0.053, n = 132 p = 0.004, n = 142 p = 0.001, n = 274		
hs-CRP-to-albumin ratio	Mean rank (n) Overall	123.13 (171)	158.56 (44)	163.45 (59)
	Test Statistics*	p = 0.001, n = 274		
White blood cell count	Mean rank (n) Female Male Overall	70.73 (97) 74.55 (95) 144.78 (192)	84.86 (25) 93.65 (23) 178.10 (48)	75.84 (25) 84.96 (41) 160.97 (66)
	Test Statistics* Female Male Overall	p = 0.325, n = 147 p = 0.0147, n = 159 p = 0.049, n = 306		

Note: *Kruskal–Wallis *H*-test.
Abbreviations: IMT, intima-media thickness; hs-CRP, high-sensitive C reactive protein.

The Relation Between Femoral Arterial IMT and Plasma Hs-CRP Levels

High-sensitive CRP, an acute phase of the inflammatory marker, might relate to an increased risk of cardiovascular diseases and incident metabolic syndrome.[13,43,44] High-sensitive CRP could reduce nitric oxide (NO) bioavailability, which induces endothelial and cardiovascular dysfunctions.[45,46] In our study, there was a significant difference in hs-CRP levels among different IMT groups. An increase in hs-CRP levels significantly correlated to thickened IMT of the femoral artery. Studies have shown that hs-CRP is associated with peripheral arterial disease in patients with type 2 diabetes. Serum hs-CRP seems to be associated with a low ankle-brachial pressure index (ABPI <0.9).[47] High-sensitive CRP is also produced at the area of atherosclerotic plaques of lower limb arteries.[48] Moreover, a positive association has been reported between hs-CRP levels and direct risk factors for atherosclerosis such as age, smoking, body mass, total cholesterol, lipoprotein a, fibrinogen and homocysteine.[49] Secreted frizzled-related protein (SFRP-5) which appears to be an anti-inflammatory adipokine and a modulator of metabolic dysfunction contributes to preventing obesity, insulin resistance, cardiovascular disease, and diabetes mellitus.[50,51] Other studies showed that the association between a low level of SFPR5 and an increase in hs-CRP are independent biomarkers for risk stratification in heart failure in patients with T2DM.[52,53]

Table 3 Univariate and Multivariate Linear Regression Analysis: Standardized Beta Coefficients of Independent Variables and Femoral Intimal Media Thickness

Variables, Unit	Univariate		Multivariate		
	r	*P*-value	Standardized Beta	*P*-value	VIF
Age, years	0.434	*0.000*	0.311	*0.000*	1.96
Waist circumference, cm	0.187	*0.001*			
WHR	0.15	*0.009*			
BMI, kg/m²	0.085	0.136	−0.092	0.192	1.32
SBP, mmHg	0.265	*0.000*	0.275	*0.002*	2.14
DBP, mmHg	0.129	*0.024*	−0.156	0.076	2.06
FPG, mmol/L	0.05	0.387	0.081	0.223	1.17
Total cholesterol, mmol/L	0.113	*0.048*	0.079	0.243	1.23
HDL-C, mmol/L	−0.05	0.391	−0.091	0.147	1.06
Albumin, g/L	−0.182	*0.001*	−0.151	*0.029*	1.27
hs-CRP, mg/L	0.278	*0.000*	0.163	*0.024*	*1.39*
fGLP-1, pmol/L	−0.362	*0.000*			
eGFR, mL/min	−0.176	*0.002*	0.078	0.351	1.89
24hUA, mg/L	0.229	*0.001*	0.100	0.130	1.16
White blood cell, G/L	0.088	0.124	0.170	*0.015*	1.30
Red blood cell, T/L	−0.169	*0.003*	−0.125	0.070	1.27
Potassium, mmol/L	−0.067	0.246	0.131	*0.042*	1.10

Note: *P*-values in italics were significant.
Abbreviations: VIF, variance inflation factor; WHR, waist-to-hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitive C reactive protein; fGLP-1, fasting glucagon-like peptide-1; 24hUA, 24-h urinary albumin; eGFR, estimated glomerular filtration rate.

Table 4 The Multivariate Logistic Regression Analysis Associated Other Factors with Abnormal IMT and Atherosclerosis of Femoral Artery

Variables, Unit	Abnormal IMT (Thick IMT and Atherosclerosis)				Atherosclerosis			
	B	p	OR	95% CI	B	p	OR	95% CI
Albumin, g/L	−0.180	*0.028*	0.84	0.71–0.98	−0.236	*0.018*	0.79	0.65–0.96
White blood cell count, G/L	0.366	*0.003*	1.44	1.13–1.83	0.31	*0.033*	1.36	1.03–1.81
hs-CRP, mg/L	0.079	*0.036*	1.08	1.01–1.16	0.088	*0.026*	1.09	1.01–1.18
SBP, mmHg	0.071	*0.007*	1.07	1.02–1.13	0.091	*0.005*	1.10	1.03–1.17
LDLC, mmol/L	0.080	0.764	1.08	0.64–1.82	0.042	0.897	1.04	0.55–1.98
2hr-PPG, mmol/L	−0.026	0.644	0.97	0.87–1.09	−0.124	0.141	0.88	0.75–1.04
Cpeptide, nmol/L	−0.693	0.211	0.50	0.17–1.48	−0.141	0.812	0.87	0.27–2.78
Potassium ion, mmol/L	1.058	0.142	2.88	0.70–11.82	1.044	0.186	2.84	0.60–13.37
DBP, mmHg	−0.083	*0.036*	0.92	0.85–0.99	−0.133	*0.007*	0.88	0.80–0.96
Hemoglobin, g/L	0.024	0.253	1.02	0.98–1.07	0.043	0.096	1.04	0.99–1.10
24hUA, mg/L	0.007	0.409	1.01	0.99–1.03	0.009	0.320	1.01	0.99–1.03
Hosmer and Lemeshow Test	$\chi^2(8) = 5.527$; p = 0.70, n = 102				$\chi^2(8) = 9.926$; p = 0.27, n = 90			

Note: *P*-values in italics were significant.
Abbreviations: hs-CRP, high-sensitive C reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; 2hr-PPG, two-hour postprandial glucose; LDL-C, low-density lipoprotein cholesterol; 24hUA, 24-h urinary albumin.

This study showed that hs-CRP levels increased significantly in male patients with thickened femoral arterial IMT or atherosclerosis, similar to the data of albumin level. The ratio between hs-CRP and albumin was high in the thickened IMT and atherosclerosis compared with normal IMT. This correlation suggests that a decrease in albumin levels and an increase in hs-CRP play an important role in endothelial dysfunction and atherosclerosis. In patients with type 2 diabetes,

serum hs-CRP/albumin ratio was significantly higher in complicated diabetic patients compared with the control group.[7] Another study showed that the hs-CRP/albumin ratio is useful to evaluate prognosis and mortality in many diseases.[54] Additionally, the hs-CRP-to-albumin ratio was associated with all-cause in-hospital mortality among patients older than 65 years[55] and played a role in the pathogenesis of slow coronary flow.[22]

The Relation Between Femoral Arterial IMT and White Blood Cell Count

White blood cell count, a routinely available marker of inflammation, is associated with macro- and microvascular complications[56] and is known to be involved in vascular damage and atherosclerosis,[57,58] mediated the association between increased arterial stiffness and risk of type 2 diabetes mellitus.[18] In our study, there was a significant difference in white blood cell count among different IMT groups, and the increase in white blood cell count significantly correlated with IMT and thickened femoral arterial IMT. However, there was no significant difference between men and women. Another study showed that impaired endothelium-dependent dilation was associated with increased numbers of neutrophils, eosinophils, and monocytes mediated by the decreased response to NO and myeloperoxidase-associated reductions in tetrahydrobiopterin and NO bioavailability.[59] White blood cell, neutrophil, and eosinophil count are the independent predictors of increased cardiovascular risk in the adolescent population.[60] White blood cell count is linked to carotid and femoral atherosclerosis.[61]

The present study showed that, in the univariate linear regression analysis, the femoral arterial IMT positively correlated to hs-CRP levels and white blood cell count, and negatively correlated to albumin levels. In the multivariate logistic regression analysis, these factors also correlated to abnormal femoral arterial IMT (including thick IMT and atherosclerosis) and atherosclerosis in nT2D. Inflammatory biomarkers such as higher concentrations of hs-CRP, higher white blood cell count and lower serum albumin levels are associated with weight gain, increasing body fat,[62,63] and increased risk of cardiovascular disease.[10,33] Specifically, high hs-CRP level and white blood cell count, and low serum albumin level are independent risk factors for endothelial dysfunction and cardiovascular disease.[33] Since higher concentrations of hs-CRP, higher white blood cell count, and lower serum albumin levels could predict changes in arterial IMT and atherosclerosis.

This study has limitations. This study was just an observational and cross-sectional design since causality can not be confirmed. Moreover, we did not measure the thickness of the femoral artery wall, albumin levels, hs-CRP levels, and white blood cell count in the control group.

Conclusion

In conclusion, there was a significant difference in albumin, hs-CRP levels, hs-CRP-to-albumin ratio, and white blood cell count between the different femoral arterial IMT groups (namely normal IMT, thick IMT, and atherosclerosis) and these factors correlated to IMT of the femoral artery. Reduced plasma albumin, high hs-CRP, and elevated white blood cell count increased the odds for atherosclerosis of the femoral artery.

Abbreviations

hs-CRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; nT2D, newly-diagnosed type 2 diabetes mellitus; WHR, waist-to-hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2h-PPG, two-hour postprandial glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; fGLP-1, fasting glucagon-like peptide-1; AST, aspartate transferase; ALT, alanine transferase; 24hUA, 24-h urinary albumin; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval; SD, standard deviation; VIF, variance inflation factor.

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All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article was submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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