https://doi.org/10.46389/rjd-2023-1270
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2023; volume 30, issue 4, pages 380–389

Original Article

The relationship between fibrinogen levels, inflammatory biomarkers and peripheral arterial disease risk factors in patients with metabolic syndrome from Northwestern Algeria

Imane Bouragba [1]*, Mustapha Diaf [2]

[1] Department of Biology, Laboratoire de MicrobiologieMoléculaire, Protéomics et Santé, Faculty of Natural and Life Sciences, Djillali LIABES University, Sidi-Bel-Abbes, Algeria

[2] Department of Biology, Laboratoire de Nutrition, Pathologie, Agrobiotechnologie et Santé, Faculty of Natural and Life Sciences, Djillali LIABES University, Sidi-Bel-Abbes, Algeria

* Correspondence to: Imane Bouragba, Department of Biology, Laboratoire de MicrobiologieMoléculaire, Protéomics et Santé, Faculty of Natural and Life Sciences, Djillali LIABES University, PO. BOX 89, Sidi-Bel-Abbes 22000, Algeria. Phone: +213 698871740; E-mail: imane.bouragba@univ-sba.dz

Received: 1 February 2023/ Accepted: 17 August 2023

Abstract

Risk factors for peripheral arterial diseases (PAD) are smoking, diabetes, hypertension and dyslipidemia, which are components of metabolic syndrome (MetS). Our objective was to investigate the role of inflammatory biomarkers and plasma fibrinogen levels in the association of PAD with MetS. A cross-sectional comparative study including patients with and without PAD was conducted for five months. The diagnosis of PAD was made by an ankle-brachial index (ABI) <0.9 and confirmed by angiography. MetS was defined according to NCEP ATPIII criteria and raised fibrinogen levels were defined as plasma fibrinogen ≥4 mg/l. Of a total of 518 patients, 15.6% had PAD. In PAD patients, waist circumference, systolic and diastolic pressure, lipid profile and fibrinogen levels were significantly higher ($p<0.05$). Binary logistic regression revealed that the male gender was more at risk of PAD, and tobacco is a powerful predictor of PAD (OR=3.04). Cardiovascular disease and PAD each highlighted significant contributions to fibrinogen control ($p<0.001$); diabetics and smokers were, respectively, 2.03[1.15–3.47] and 1.58[0.78–3.19] times more at risk of poor fibrinogen control. 14.1% with MetS developed PAD *versus* 1.5% without MetS ($p<0.001$). In conclusion, high fibrinogen levels in Mets increase the risk of PAD. Peripheral arterial disease prevention may be involved in correcting MetS components and controlling fibrinogen levels.

Keywords: peripheral arterial diseases, metabolic syndrome, inflammation, fibrinogen.

Introduction

Peripheral artery diseases (PAD) are systemic inflammations that affect all peripheral arteries except the coronaries [1]. They form a marker of increased cardiovascular risk; most are caused by atherosclerosis [2, 3]. PAD is associated with a high rate of mortality and morbidity; the amputation rate is five times higher in diabetics, and mortality is five times earlier and higher in this population [2, 4]. The prevalence of PAD is increasing worldwide, and the majority of cases are asymptomatic; it represents 2 to 10% of the general population and 20% of patients over 70 years old [5].

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including hypertension, abdominal obesity, insulin resistance, and atherogenic dyslipidemia [6]. Previous research shows that MetS is associated with elevated levels of inflammatory and hemostatic biomarkers, such as C – reactive protein (CRP) and fibrinogen. In 1950, it was found that high serum fibrinogen concentration is associated with a risk of cardiovascular diseases (CVD), including PAD [7–9]. Globally, the most important risk factors for PAD are smoking, diabetes, hypertension and high levels of low-density lipoprotein and cholesterol, which are components of MetS. Although, the magnitude of these associations is higher in high-income countries than in low- and middle-income countries [10]. The risk of developing arterial disease is four times higher in people with diabetes than in the general population [11].

Recently, the understanding of atherogenesis has expanded to include inflammation as a major contributor to the initiation and progression of atherosclerosis [12, 13]. Therefore, this study aimed to investigate the role of inflammatory biomarkers and plasma fibrinogen levels in the association of PAD with MetS.

Material and methods

We underwent a transversal observational study on patients admitted between January 2019 and March 2022 to the internal medicine unit of the public hospital establishment of "Ben Badis" and to the Public Establishment of Local Health (Larbi Ben M'hidi Diabetes Centre) in the Wilaya of Sidi-Bel-Abbes in Northwestern Algeria.

Data collection

The patient's medical records were reviewed for medical history, symptoms and signs, biochemical parameters, and complications of diabetes, hypertension, dyslipidemia, and cardiovascular diseases. All patients with complete and adequate medical records were involved in the analysis. Patients with cancer or autoimmune diseases were excluded. All patients' anthropometric parameters and body weight (in kg) were measured using an electronic balance, and height (in meters) was measured through a body meter. The body mass index (BMI) was calculated as follows: BMI (Kg/m^2) = weight (Kg) / height ^{2} (m^2). Waist circumference was measured with a tape measure. A sphygmomanometer measured blood pressure. The latest biochemical assessment including glycated hemoglobin (HbA1c), fasting glycemia, urea, creatinine, albuminemia, CRP, D.dimer, creatinine clearance, fibrinogen, prothrombin and lipid parameters, namely total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides(TG), were taken from medical records. Raised fibrinogen levels were defined as a plasma fibrinogen ≥4 mg/l.

MetS and PAD definition

MetS was defined according to NCEP ATP III criteria; the ATPIII required three or more of the following five criteria: Waist circumference ≥102 cm for men or

Table 1: Baseline characteristics of the study population according to the presence or absence of peripheral arterial diseases.

	Total	NPAD	PAD	P-value
n (%)	518 (100)	437 (84.4)	81 (15.6)	
Age (years)	60.78±17.05	59.96±17.56	65.22±13.19	**0.011***
Patients' gender; n (%)				
Female	294 (56.8)	254 (49.0)	40 (7.7)	0.145 #
Male	224 (43.2)	183 (35.3)	41 (7.9)	
Corpulence; n (%)				
Underweight	19 (4.1)	18 (3.8)	1 (0.2)	**0.023** #
Normal weight	120 (25.6)	103 (22.0)	17 (3.6)	
Overweight	199 (42.4)	174 (37.1)	25 (5.3)	
Obese	131 (27.9)	100 (21.3)	31 (6.6)	
Tobacco consumption; n (%)				
Non-smoker	278 (54.2)	242 (47.2)	36 (7.0)	**0.004** #
Former smoker	76 (14.8)	63 (12.3)	13 (2.5)	
Active smoker	70 (13.6)	49 (9.6)	21 (4.1)	
Passive smoker	89 (17.3)	78 (15.2)	11 (2.1)	
Metabolic syndrome				
No	144 (27.8)	136 (26.3)	8 (1.5)	**<0.001** #
Yes	374 (72.2)	301 (58.1)	73 (14.1)	
Diabetes; n (%)				
No	85 (19.7)	70 (16.24)	15 (3.5)	0.552 #
Yes	347 (80.3)	285 (66)	62 (14.4)	

Table 1: Continued.

	Total	NPAD	PAD	P-value
Hypertensive; n (%)				
No Yes	274 (52.9%) 244 (47.1%)	247 (47.7%) 190 (36.7%)	27 (52.9%) 45 (10.4%)	**<0.001**[#]
Dyslipidemia; n (%)				
No Yes	336 (64.9) 182 (35.1)	317 (61.2) 120 (23.2)	19 (3.7) 62 (12.0)	**<0.001**[#]
Cardiovascular diseases; n (%)				
No Yes	250 (48.3) 268 (51.7)	249 (48.1) 188 (36.3)	1 (0.2) 80 (15.4)	**<0.001**[#]
Waist circumference (cm); mean±SD	100±11.60	99.93±11.54	104.24±11.33	**0.002***
Patient's systolic pressure (cmHg); mean±SD	12.38±2.24	12.25±2.16	13.01±2.54	**0.006***
Patient's diastolic pressure(cmHg); mean±SD	6.77±1.40	6.69±1.33	7.2±1.65	**0.003***
Diabetes duration (year); mean±SD	13.99±11.84	13.68±11.96	15.59±11.18	0.184*
Glycated hemoglobin (%); mean±SD	9.16±2.23	8.10±2.17	8.51±2.58	0.135*
Fasting glycaemia (g/l)	1.55±0.70	1.57±0.70	1.45±0.69	0.184*
HDLc (g/l); mean±SD	0.45±0.15	0.46±0.14	0.41±0.19	0.769*
LDLc (g/l); mean±SD	1.10±0.39	1.09±0.37	1.2±0.48	**0.037***
TC (g/l); mean±SD	1.70±0.45	1.67±0.41	1.54±0.58	**0.001***
TG (g/l); mean±SD	1.30±0.64	1.25±0.63	1.58±0.68	**<0.001***
Urea (g/l); mean±SD	0.69±0.83	0.69±0.78	0.68±1.05	0.92*
Creatinine (g/l); mean±SD	18..48±19.14	19.33±20	14.24±13.12	**<0.001***
Albuminemia (g/dl); mean±SD	21.98±19.58	22.31±19.76	20.26±18.62	0.390*
CRP (mg/l); mean±SD	40.53±41.56	41.11±42	37.49±36.37	**0.011***
D-dimer (ug/l); mean±SD	554±666.69	444.48±341	198.52±1242.95	**<0.001***
Creatinine clearance (ml/min); mean±SD	68.57±20.14	68.93±20.68	67.23±18.10	0.556*
Fibrinogen (g/l); mean±SD	4.67±3.95	3.86±2.74	8.49±6.04	**<0.001***
Prothrombin (%); mean±SD	73.54±1.55	74.63±20.11	67.92±27.36	**0.014***

Note: * – P-value for student t test; [#] – P-value for Chi-square test; p≤0.05 was considered as statistically significant. NPAD – non peripheral arterial diseases; PAD – peripheral arterial diseases; HDL – high-density lipoproteins; LDL – low-density lipoprotein; TC – total cholesterol; TG – triglycerides; CRP – C-reactive protein.

≥88 cm for women, triglycerides ≥1.5 g/l, HDL <4 g/l for men or <5 g/l for women, hypertension (systolic blood pressure ≥13 cmHg or diastolic blood pressure ≥8.5) or impaired glucose tolerance (fasting plasma glucose ≥1.1 g/l) or diabetes [14].

PAD was confirmed by angiography and an ankle-brachial index (ABI) <0.90 after having found signs of PAD during a medical exam (a weak or absence of pulse below a narrowed area of the artery, whooshing sounds over the arteries that can be heard with a stethoscope, evidence of poor wound healing in the area where blood flow is restricted and decreased blood pressure in affected limb).

Statistical analysis

Data were processed and analyzed using SPSS 20.0. Results are expressed as means±standard deviations. An independent student's t-test was used to compare mean values between patients with PAD (PAD) and patients without PAD (NPAD). A chi-square test was performed for comparing qualitative variables between

https://doi.org/10.46389/rjd-2023-1270

the two groups. Binary logistic regression was applied to investigate risk factors associated with PAD, MetS and Raised fibrinogen levels.

Results

Five hundred and eighteen subjects (224 Males and 294 Females) were recruited for this study; 72.2% were with MetS and 15.6% with PAD (Table 1). The mean age was 60.78±17.05 years. 70.3% of patients were either overweight or obese. 80.3% were diabetics, 47.1% were hypertensive, 51.7% with CVD and 35.1% of participants had dyslipidemia. Concerning their smoking status, 54.2% were non-smokers, 18.8% were former smokers, 13% were active smokers, and 17.3% were passive smokers.

Table 1 summarized the characteristics of the studied patients; a significant association was observed between PAD and the age of patients (p=0.011), waist circumference (p=0.002), smoking status (p=0,004), systolic and diastolic pressure (p=0.006, p=0.003), CRP levels (p=0.011), prothrombin levels (p=0.014) and lipid profiles except for HDL levels (LDL: p= 0.037, TC: p= 0.001, TG: p<0.001). Very significant differences were noted regarding metabolic syndrome, high blood pressure, dyslipidemia and CVD, creatinine, D.dimer and fibrinogen levels (p<0.001). However, no significant differences between gender, diabetes, diabetes duration, HbA1c, fasting glycemia, HDL levels, urea, albuminuria, and creatinine clearance concentrations (p>0.05).

We invested risk factors associated with PAD (Table 2); when binary logistic regression analysis was performed, BMI, high blood pressure, smoking, dyslipidemia, CVD, family history (diabetes, CVD and hypertension), CRP and fibrinogen levels, and MetS each highlighted a significant contribution to PAD(p<0.05). Logistic regression between these risk factors showed that the odd ratio of PAD in males was 0.70[0.44–1.13]. Therefore, men are more at risk of PAD. The odd ratios reported on hypertensive patients, diabetics, or those

Table 2: Crude "Odds Ratio" of risk factors associated with the presence or absence of peripheral arterial diseases.

Variables	NPAD, n=437 Number (%)	PAD, n=81 Number (%)	β	Odds ratio (95% CI)	P-value*
Gender					
Female	254 (49.0)	40 (7.7)	-	Reference	-
Male	183 (35.3)	41 (7.9)	-0.35	0.70[0.44–1.13]	0.146
BMI					
Normal	121 (25.8)	18 (3.8)	-	Reference	-
Overweight	174 (37.1)	25 (53)	-0.73	0.48[0.25–0.91]	0.024
Obese	100 (21.3)	31 (6.6)	-0.77	0.46[0.26–0.83]	**0.010**
High blood pressure					
Absence	247 (47.7)	27 (5.26)	-	Reference	-
Presence	190 (36.7)	81 (15.6)	0.96	0.39[0.23–3.69]	**<0.001**
Tobacco consumption					
Non-smoker	242 (47.2)	36 (7.0)	-	Reference	-
Smoker	63 (12.3)	13 (2.5)	1.11	3.04[1.35–6.85]	**0.007**
Former smoker	49 (9.6)	21 (4.1)	0.05	1.06[0.51–2.17]	0.885
Passive smoking	78 (15.2)	11 (2.1)	0.38	1.46[0.61–3.49]	0.391
Diabetes					
Absence	70 (16.24)	15 (3.5)	-	Reference	-
Presence	285 (66)	62 (14.4)	-0.02	0.99[0.53–1.83]	0.962
Dyslipidemia					
Absence	317 (61.2)	19 (3.7)	-	Reference	-
Presence	120 (23.2)	62 (12.0)	-2.15	0.12[0.067–0.20]	**<0.001**
Cardiovascular diseases					
Absence	249 (48.1)	1 (0.2)	-	Reference	-
Presence	188 (36.3)	80 (15.4)	-4.663	**0.009**[0.001–0.068]	**<0.001**

Table 2: Continued.

Variables	NPAD, n=437 Number (%)	PAD, n=81 Number (%)	β	Odds ratio (95% CI)	P-value*
Family history					
Absence	96 (24.7)	11 (2.8)	-	Reference	-
Presence	226 (58.1)	56 (14.4)	-0.77	0.46[0.23–0.92]	**0.028**
COVID infection					
Uninfected	129 (42.9)	36 (12)	-	Reference	-
Infected	109 (36.2)	27 (9)	0.12	1.13[0.643–1.973]	0.677
CRP					
<6 mg/l	142 (28.2)	16 (3.2)	-	Reference	-
≥6 mg/l	282 (56.1)	63 (12.5)	-0.68	0.50[0.28– 0.905]	**0.022**
LDLc					
<1.2 g/l	236 (50.4)	38 (8.1)	-	Reference	-
≥1.2 g/l	156 (33.3)	38 (8.1)	0.41	0.66[0.40 -1.08]	0.100
Fibrinogen					
<4 mg/l	286 (65.1)	24 (4.8)	-	Reference	-
≥4 mg/l	276 (54.9)	56 (11.1)	-2.18	0.11[0.07-0.20]	**<0.001**
HbA1c					
<7%	147 (29.2)	16 (3.2)	-	Reference	-
≥7%	282 (56.1)	63 (12.5)	-0.22	0.81[0.48–1.35]	0.411
Metabolic syndrome					
Absence	136 (26.3)	8 (1.5)	-	Reference	-
Presence	301 (58.1)	73 (14.1)	-1.42	0.24[011–0.52]	**<0.001**

Note: * – multivariate logistic regression significant at p=0.05; CI – confidence interval; NPAD – non peripheral arterial diseases; PAD – peripheral arterial diseases; BMI – body mass index; CRP – C-reactive protein; LDL – low-density lipoprotein; HbA1c – glycated hemoglobin.

infected with COVID were, respectively, 0.39[0.23–3.69], 0.99[0.53–1.83], and 1.13[0.64–1.97]. Likewise, elevated LDL (≥1.2 g/l) levels and HbA1c (≥7%) disclosed odd ratios of 0.66[0.40–1.08] (p=0.1) and 0.81[0.48–1.35], respectively. Tobacco conception is a powerful predictor of PAD with an odd ratio of 3.04[1.35–6.85].

The risk of having elevated fibrinogen levels according to various risk factors was estimated through odds ratios (Table 3). 29% of participants had fibrinogen levels higher than 4 mg/l. Dyslipidemia, CVD, and PAD each highlighted higher significant contributions to the fibrinogen control (p<0.001); furthermore, very

Table 3: Crude "Odds Ratio" of risk factors associated with fibrinogen control.

Variables	Fibrinogen <4 mg/l, n=309 Number (%)	Fibrinogen ≥4 mg/l, n=130 Number (%)	β	Odds ratio (95% CI)	P-value*
Gender					
Female	184 (41.9)	67 (15.3)	-	Reference	-
Male	125 (28.5)	63 (14.3)	-0.33	0.72[0.48–1.20]	0.12
BMI					
Normal	82 (20.8)	32 (8.1)	-	Reference	-
Overweight	122 (31)	50 (12.7)	0.25	0.78[0.44–1.38]	0.396
Obese	72 (18.3)	36 (9.1)	0.20	0.82[0.49–1.38]	0.452

https://doi.org/10.46389/rjd-2023-1270

Table 3: Continued.

Variables	Fibrinogen <4 mg/l, n=309 Number (%)	Fibrinogen ≥4 mg/l, n=130 Number (%)	β	Odds ratio (95% CI)	P-value*
High blood pressure					
Absence	175 (39.9.7)	53 (12.1)	-	Reference	-
Presence	134 (30.5)	77 (17.5)	-0.64	0.53[0.35–0.80]	**0.030**
Tobacco consumption					
Non-smoker	35 (8)	25 (5.7)	-	Reference	-
Smoker	176 (40.5)	62 (14.3)	0.47	1.58[0.78–3.19]	0.205
Former smoker	42 (9.7)	18 (4.1)	-0.25	0.78[0.44–1.37]	0.382
Passive smoking	53 (12.2)	24 (5.8)	-0.55	0.95[0.46–1.97]	0.883
Diabetes					
Absence	40 (10.9)	31 (8.4)	-	Reference	-
Presence	215 (58.4)	82 (22.3)	0.71	2.03[1.15–3.47]	**0.009**
Dyslipidemia					
Absence	215 (49)	66 (15)	-	Reference	-
Presence	94 (21.4)	64 (14.6)	-0.80	0.45[0.30–0.69]	**<0.001**
Cardiovascular diseases					
Absence	177 (40.3)	20 (4.6)	-	Reference	-
Presence	132 (30.1)	110 (25.1)	-1.99	0.14[0.08–0.23]	**<0.001**
Family history					
Absence	63 (18.9)	21 (6.3)	-	Reference	-
Presence	162 (48.6)	87 (26.1)	-0.48	0.62[0.36–1.09]	0.094
COVID infection					
Uninfected	93 (35.8)	48 (18.5)	-	Reference	-
Infected	76 (29.2)	43 (16.5)	-0.09	0.92[0.54–1.52]	0.725
CRP					
<6 mg/l	104 (14.4)	23 (5.4)	-	Reference	-
≥6 mg/l	194 (45.5)	105 (24.6)	-0.90	0.41[0.25–0.65]	**0.001**
LDLc					
<1.2 mg/l	167 (42.2)	62 (15.7)	-	Reference	-
≥1.2 mg/l	111 (28)	56 (14.1)	-0.31	0.74[0.48–1.14]	0.17
HbA1c					
<7%	104 (24.4)	41 (9.6)	-	Reference	-
≥7%	195 (45.8)	86 (20.2)	-1.11	0.90[0.57–1.39]	0.62
PAD					
Absence	286 (65.1)	76 (17.3)	-	Reference	-
Presence	23 (5.2)	54 (12.3)	-2.18	0.11[0.07–0.20]	**<0.001**
Metabolic syndrome					
Absence	92 (21)	23 (5.2)	-	Reference	-
Presence	217 (49.4)	107 (24.4)	-0.68	0.51[0.30–0.85]	**0.009**

Note: * – multivariate logistic regression significant at p=0.05; CI – confidence interval; BMI – body mass index; CRP – C-reactive protein; LDL – low-density lipoprotein; HbA1c – glycated hemoglobin; PAD – peripheral arterial diseases.

significant values for diabetes, CRP levels, MetS, and high blood pressure ($p<0.01$) were plotted. Diabetic and smoker patients were, respectively, 2.03[1.15–3.47] and 1.58[0.78–3.19] times more at risk of poor fibrinogen control compared to non-diabetics and nonsmokers. Males, overweight, obese, and COVID-19-infected subjects and those with a family history or increased LDL, HDL, and HbA1c levels had higher fibrinogen levels, but this association was insignificant ($p>0.05$).

Table 4 shows the odd ratios of risk factors associated with the presence or absence of MetS. For the whole risk factors, the logistic regression analysis revealed a significant contribution to MetS ($p<0.05$) except for four factors (gender, smoking, COVID-19 infection and elevated LDL levels) ($p>0.05$). The odd ratios of MetS in males and patients with elevated LDL levels were, respectively, 0.88[0.60–1.30] and 1.00[0.65–1.53]. Smoking was highlighted as an important risk factor for MetS, with an odd ratio of 1.22[0.73–2.05] for former smokers and 1.87[0.91–3.84] for passive smoking. 14.1% with MetS developed PAD and 1.5% without MetS ($p<0.001$).

Discussion

In the present study, we set out to examine the risk of PAD in a sample of patients with or without MetS. The overall prevalence of MetS was 72.7%; this finding is comparable with results from Mexico [15, 16]. However, it is high compared to those obtained from north India (40.9%) [17], Morocco (35.73%) [18], Cameroon (32.45%) [19], Tunisia (30%) [20], western Romania (27.7%) [21] and South Africa (21.8%) [6]. The high prevalence of MetS may be caused by the high prevalence of diabetic (80.3%) and hypertensive (47.1%) subjects in our population. 14.1% of patients with MetS developed PAD and 1.5% without MetS ($p<0.001$); this finding is similar to the result from Bangui (Central Africa) (15%) [22] and included in interval plotted by the Western studies (4–19%) [23], however, it is low than those disclosed from India (26.74%) [10]. Marocco 28.94% [24] and Brazzaville (Congo) (32.4%) [22].

This study shows that the subjects with PAD were older than those without PAD (65.22±13.19 *vs.* 59.96±17.56, respectively, ($p= 0.011$) and a significant difference in terms of corpulence, smoking, hypertension, Dyslipidemia, markers of inflammation and thrombosis between the two groups, a similar finding reported by Celebi S [6] and Alexandr Ceasovschih [1].

Male gender, BMI, high blood pressure(hypertension), smoking, dyslipidemia, CVD, family history, diabetes, LDL, HbA1c, CRP levels and MetS each highlighted a significant contribution to PAD in our investigation, compared results reported by previous studies [25–28]. Patients with MetS are at increased risk for PAD, but this association is not mediated by inflammation; the same observation has been suggested by Himabindu Vidula [29]; this result can be explained by taking anti-inflammatory treatments. Tobacco conception is a powerful predictor of PAD in our population; many studies have confirmed that smoking is a potent risk factor for PAD [26, 30]. COVID-19 is a unique thrombo-inflammatory condition, and diabetic and hypertensive patients are more susceptible to PAD [31], which was consistent with our findings.

Fibrinogen was positively correlated with the prevalence of PAD in T2D patients [25]. Age, systolic blood pressure, smoking, CRP levels, and abdominal obesity contribute to the development of elevated levels of fibrinogen, which proved to be a significant predictor

Table 4: Crude "Odds Ratio" of risk factors associated with the presence or absence of metabolic syndrome.

Variables	Without MetS, n=144 Number (%)	With MetS, n=374 Number (%)	β	Odds ratio (95% CI)	P-value*
Gender					
Female	85 (16.4)	209 (40.3)	-	Reference	-
Male	59 (11.4)	165 (31.9)	-0.13	0.88[0.60–1.30]	0.518
BMI					
Normal	70 (14.9)	69 (14.7)	-	Reference	-
Overweight	41 (8.7)	158 (33.7)	-2.14	0.12[0.06–0.23]	**<0.001**
Obese	14 (3.6)	117 (24.9)	-0.77	0.46[0.24–0.89]	**0.020**
High blood pressure					
Absence	133 (25.7)	41 (27.2)	-	Reference	-
Presence	11 (2.1)	233 (45)	-2.99	0.04[0.01–0.25]	**0.001**

https://doi.org/10.46389/rjd-2023-1270

Table 4: Continued.

Variables	Without MetS, n=144 Number (%)	With MetS, n=374 Number (%)	β	Odds ratio (95% CI)	P-value*
Tobacco consumption					
Non-smoker	23 (4.5)	47 (9.2)	-	Reference	-
Smoker	76 (14.8)	202 (39.4)	-0.06	0.94[0.48–1.83]	0.851
Former smoker	15 (2.3)	61 (11.9)	0.20	1.22[0.73–2.05]	0.453
Passive smoking	28 (5.5)	61 (11.9)	0.62	1.87[0.91–3.84]	0.090
Diabetes					
Absence	43 (10)	42 (9.7)	-	Reference	-
Presence	53 (12)	294 (68.1)	-1.73	0.18[0.11–0.30]	**<0.001**
Dyslipidemia					
Absence	135 (26.1)	201 (38.8)	-	Reference	-
Presence	9 (1.7)	173 (33.4)	-2.56	0.08[0.04–0.16]	**<0.001**
Cardiovascular diseases					
Absence	110 (21.2)	140 (27)	-	Reference	-
Presence	34 (6.64)	234 (45.2)	-1.69	0.19[0.12–0.29]	**<0.001**
Family history					
Absence	50 (12.9)	57 (14.7)	-	Reference	-
Presence	75 (19.3)	207 (53.2)	-0.88	0.41[0.26–0.66]	**<0.001**
COVID infection					
Uninfected	48 (15.9)	117 (38.9)	-	Reference	-
Infected	29 (9.6)	107 (35.5)	-0.42	0.66[0.39–1.12]	0.125
CRP					
<6 mg/l	54 (10.7)	104 (20.7)	-	Reference	-
≥6 mg/l	78 (15.5)	267 (53.1)	-0.58	0.56[0.37–0.85]	**0.007**
LDLc					
<1.2 mg/l	68 (14.5)	206 (44)	-	Reference	-
≥1.2 mg/l	48 (41.4)	146 (41.5)	-0.004	1.00[0.65–1.53]	0.985
HDLc					
Normal	93 (19.4)	140 (29.2)	-	Reference	-
Low	26 (5.4)	221 (46)	-1.73	0.18[0.11–0.29]	**<0.001**
TG					
<1.5 g/l	124 (23.9)	156 (30.1)	-	Reference	-
≥1.5 g/l	2 (3.9)	218 (42.1)	-2.16	0.12[0.07–0.19]	**<0.001**
HbA1c					
<7%	58 (11.5)	113 (22.5)	-	Reference	-
≥7%	81 (16.1)	251 (49.9)	-0.46	0.63[0.42–0.94]	**0.024**
Fibrinogen					
<4 mg/l	92 (21)	217 (49.4)	-	Reference	-
≥4 mg/l	23 (5.2)	107 (24.4)	-0.68	0.51[0.30–0.85]	**0.009**
PAD					
Absence	136 (26.3)	301 (58.1)	-	Reference	-
Presence	8 (1.5)	73 (14.1)	-1.42	0.24[0.11–0.52]	**<0.001**

Note: * – multivariate logistic regression significant at p=0.05; CI – confidence interval; BMI – body mass index; CRP – C-reactive protein; LDL – low-density lipoprotein; HDL – high-density lipoproteins; TG – triglyceride; HbA1c – glycated hemoglobin; PAD – peripheral arterial diseases.

of MetS risk among men, likely even independent of the MetS components [32]. HbA1c significantly affects plasma fibrinogen in diabetics [33, 34]; similar findings were observed in our study, in which diabetics and smokers are at increased risk of having elevated fibrinogen levels in our sample. Males, overweight, obese and COVID-infected subjects and those with a family history or increased LDL, HDL and HbA1c levels were associated with higher fibrinogen levels; fibrinogen levels were increased in patients with PAD compared to those without PAD (8.49±6.04 *vs*. 3.86±2.74 p<0.001), and the prevalence of PAD was high (12.3%) in the fibrinogen ≥4 mg/l group compared to those in the fibrinogen <4 mg/l group (5.2%). However, non-smokers showed higher fibrinogen levels than smokers (4.46±1.88 mg/dL *vs*. 3.35±1.75 mg/dL) with a statistically significant difference (p=0.043) [33].

Regarding risk factors of MetS, Abdominal obesity, HBP, smoking, diabetes, CVD, family history, elevated CRP, HDL, TG, and HbA1c levels were associated with the presence of MetS similar observation reported in a Romanian study (Bucharest) [35]. Seventy-three of our participants with MetS developed PAD compared to eight participants without MetS, and 107 subjects with MS had fibrinogen levels ≥4 mg/l compared to 23 only with fibrinogen levels <4 mg/l, proves that MetS is associated with an increased risk of PAD. Previous studies confirmed this association [36–38]; however, in another study, there was no difference in the fibrinogen level between patients with and without MetS [39].

Some limitations of the present study should be mentioned. First, data are observational; relationships reported between the risk factors and diseases cannot be construed as causal. Second, the generalization of our results to other populations may be limited because the prevalence of MetS components varies across populations. Third, MetS has been criticized partly because identifying and treating MetS may be less important than identifying and treating the individual components of MetS [40, 41]. Fourth: Dyslipidemia and hypertension treatment (statins and antihypertensive drugs, respectively) could affect lipid profile and levels of CRP, fibrinogen and uric acid. Furthermore, statins and antihypertensive drugs improve renal function, lower the risk of vascular events, and improve the survival of PAD [42, 43].

Conclusion

This study shows a high prevalence of MetS in our study population and a significant association between MetS and PAD. Elevated fibrinogen levels (≥4 mg/l) in patients with MetS increase the risk of PAD, but this association is not mediated by inflammation. It is concluded that the prevention of PAD may be involved in correcting the components of MetS and controlling fibrinogen levels. Further study is needed to determine whether inflammatory biomarkers are associated with the risk of PAD in subjects with MetS.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ceasovschih A, Sorodoc V, Onofrei V*et al*. Biomarker Utility for Peripheral Artery Disease Diagnosis in Real Clinical Practice:A Prospective Study. Diagnostics 10 (9): 723-738, 2020.
2. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and non-diabetic patients: a comparison of severity and outcome. Diabetes Care 24(8):1433-1437, 2001.
3. Criqui MH, Langer RD, Fronek A, *et al*. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 326(6):381-386, 1992.
4. Bainton D, Sweetnam P, Baker I, Elwood P. Peripheral vascular disease: consequence for survival and association with risk factors in the Speedwell prospective heart disease study. Br Heart J 72(2):128-132,1994.
5. Shu J, Santulli G. Update on peripheral artery disease: Epidemiology and evidence-based facts. Atherosclerosis 275: 379-381, 2018.
6. Celebi S, Berkalp B, Amasyali B. The association between thrombotic and inflammatory biomarkers and lower-extremity peripheral artery disease. Int Wound J 17(5): 1346-1355, 2020.
7. McDonald L, EdgillM. Coagulability of the blood in ischaemic heart disease. The Lancet 270(6993): 457-460,1957.
8. Ji X, Leng XY, Dong Y *et al*. Modifiable risk factors for carotid atherosclerosis: a meta-analysis and systematic review. Ann Transl Med 7(22): 632-646, 2019
9. Samir G M, Khalil O A, Fawzy M S, Sadek A M. Study of fibrinogen level in acute ischemic stroke patients in medical intensive care unit. Egyptian Journal of Critical Care Medicine 7(2and3): 51-56, 2020.
10. Krishnan MN, Geevar Z, Mohanan PP, Venugopal K, Devika S. Prevalence of peripheral artery disease and risk factors in the elderly: A community based cross-sectional study from northern Kerala India. Indian Heart Journal 70(6): 808-815, 2018.
11. Lepäntalo M, Apelqvist J, Setacci C, *et al*. Diabetic foot. Eur J Vasc Endovasc Surg 42(S2):60-74, 2011.
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 105(9): 1135-1143, 2002.
13. Gerhard-Herman MD, Gornik HL, Barrett C, *et al*. 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart

 https://doi.org/10.46389/rjd-2023-1270

Association Task Force on Clinical Practice Guidelines, Circulation 135(12): 686-725, 2017.
14. Heng D, Ma S, Lee JJ, *et al*. Modification of the NCEP ATP III definitions of the metabolic syndrome for use in Asians identifies individuals at risk of ischemic heart disease. Atherosclerosis 186(2):367-373, 2006.
15. Gonzalez-Mejia ME, Porchia LM, Torres-Rasgado E, *et al*.C-Peptide Is a Sensitive Indicator for the Diagnosis of Metabolic Syndrome in Subjects from Central Mexico. Metab Syndr Relat Disord. 14(4): 210-216, 2016.
16. Isordia-Salas I, Santiago-Germán D, Rodrìguez-Navarro H, *et al*. Prevalence of Metabolic Syndrome Components in an Urban Mexican Sample: Comparison between Two Classifications. Exp Diabetes Res 2012: 1-8, 2012.
17. Khan Y, Lalchandani A, Gupta AC, Khadanga S, Kumar S. Prevalence of metabolic syndrome crossing 40% in Northern India: Time to act fast before it runs out of proportions. J Family Med Prim Care 7(1):118-123, 2018.
18. El Brini O, Akhouayri O, Gamal A, Mesfioui A, Benazzouz B. Prevalence of metabolic syndrome and its components based on a harmonious definition among adults in Morocco. Diabetes Metab Syndr Obes 7:341-346, 2014.
19. Belfki H, Ali SB, Aounallah-Skhiri H, *et al*. Prevalence and determinants of the metabolic syndrome among Tunisian adults: results of the Transition and Health Impact in North Africa (TAHINA) project. Public Health Nutrition 16(4): 582-590,2013.
20. Owolabi E O, Goon D T, Adeniyi O V, Adedokun A O, Seekoe E. Prevalence and correlates of metabolic syndrome among adults attending healthcare facilities in eastern cape, South Africa. The Open Public Health Journal 10:148–159, 2017.
21. Șerban V, Diaconu L, Timar R, Vlad A. Epidemiology of the metabolic syndrome in the adult population in the city of timişoara. Romanian Journal of Diabetes Nutrition and Metabolic Diseases 16(1): 1-10, 2009.
22. Guerchet M, Aboyans V, Mbelesso P, *et al*. Epidemiology of peripheral artery disease in elder general population of two cities of Central Africa: Bangui and Brazzaville. Eur J Vasc Endovasc Surg 44 (2):164-169, 2012.
23. Ostchega Y, Paulose-Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999-2004. J Am Geriatr Soc 55(4): 583-589, 2007.
24. Mouadili M, Mbauchy C, Benzeroual D, Karimi S, El Hattaoui M, Peripheral arterial disease of the lower limbs in Moroccan hypertensive non-diabetic patients. Archives of Cardiovascular Diseases Supplements 11(3): 344, 2019.
25. Chen Q, Cao D, Ye T, Deng H, Zhu H. Peripheral Arterial Disease in Type 2 Diabetes Is Associated with an Increase in Fibrinogen Levels. Int J Endocrinol 2018: 1-8, 2018.
26. Wang Z, Wang X, Hao G, *et al*. A national study of the prevalence and risk factors associated with peripheral arterial disease from China: The China Hypertension Survey, 2012–2015. Int J Cardiol 275: 165-170: 2018.
27. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol 14(3):156-170,2017.
28. Cedarbaum E, Ma Y, Scherzer R, *et al*. Contributions of HIV, hepatitis C virus, and traditional vascular risk factors to peripheral artery disease in women. AIDS 33(13):2025-2033, 2019.
29. Vidula H, Liu K, Criqui MH, *et al*. Metabolic syndrome and incident peripheral artery disease - the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 243(1):198-203, 2015.
30. Criqui MH, Langer RD, Fronek A, *et al*. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 326(6): 381-386, 1992.
31. Rastogi A, Dogra H, Jude EB. COVID-19 and peripheral arterial complications in people with diabetes and hypertension: A systematic review. Diabetes Metab Syndr 15(5):102204, 2021.
32. Onat A, Ozhan H, Erbilen E, *et al*. Independent prediction of metabolic syndrome by plasma fibrinogen in men, and predictors of elevated levels. Int J Cardiol 135(2): 211-217, 2009.
33. Abdul Razak MK, Sultan AA. The importance of measurement of plasma fibrinogen level among patients with type- 2 diabetes mellitus. Diabetes Metab Syndr 13(2):1151-1158, 2019.
34. G Santhini, Anuradha G,Sumathy S, Sandeep U, Dhanvarshini S. Study to Evaluate the Correlation Between Coagulation Factor, Glycemic Control and the Severity of Diabetic Foot Ulcers Among South Indian Population: A Case Control Study, Romanian Journal of Diabetes Nutrition and Metabolic Diseases 27 (4), 342-48, 2020.
35. Vasilescu R, Silvia I, Constantin I T, Sorin S, A Muresan. The association between adiponectin, leptin, proinflammatory markers and metabolic syndrome in obese, non-diabetic subjects. Romanian Journal of Diabetes Nutrition and Metabolic Diseases 18 (2), 117-129, 2011.
36. Li Y, Zhao L, Yu D, Wang Z, Ding G. Metabolic syndrome prevalence and its risk factors among adults in China: A nationally representative cross-sectional study. PLoS One 13(6): e0199293, 2018.
37. Garg PK, Biggs ML, Carnethon M, *et al*. Metabolic syndrome and risk of incident peripheral artery disease: the cardiovascular health study. Hypertension 63(2):413-419, 2014.
38. Vidula H, Liu K, Criqui MH, *et al*. Metabolic syndrome and incident peripheral artery disease - the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 243(1):198-203, 2015.
39. Maksimovic M, Vlajinac H, Radak D, Marinkovic J, Jorga J. Relationship between peripheral arterial disease and metabolic syndrome. Angiology 60(5): 546-553, 2009.
40. Pratley RE. Metabolic syndrome: why the controversy?. CurrDiab Rep 7(1): 56-59, 2007.
41. Reaven GM. The metabolic syndrome: time to get off the merry-go-round? J Intern Med 269(2):127-136, 2011.
42. Schillinger M, Exner M, Mlekusch W, *et al*. Statin therapy improves cardiovascular outcome of patients with peripheral artery disease. Eur Heart J 25(9):742-748, 2004.
43. Daskalopoulou SS, Daskalopoulos ME, Liapis CD, Mikhailidis DP. Peripheral arterial disease: a missed opportunity to administer statins so as to reduce cardiac morbidity and mortality. Curr Med Chem 12(4): 443-452, 2005.