ASSOCIATION BETWEEN PERIPHERAL ARTERIAL DISEASES AND METABOLIC SYNDROME IN PATIENTS WITH TYPE 2 DIABETES FROM NORTHWESTERN ALGERIA

Imane Bouragba, Mustapha Diaf✉

Department of Biology, Laboratoire de Microbiologie Moléculaire, Protéomics et Santé, Faculty of Natural and Life Sciences, Djillali LIABES University, Sidi-Bel-Abbes, Algeria.

Address for correspondence:
Mustapha Diaf
Department of Biology, Laboratoire de Microbiologie Moléculaire, Protéomics et Santé, Faculty of Natural and Life Sciences, Djillali LIABES University, Sidi-Bel-Abbes, Algeria.

E-mail:
diafmustapha@gmail.com

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ABSTRACT

Objective: This study aims to explore the correlation between peripheral arterial diseases (PAD) and individual components of metabolic syndrome among type 2 diabetic patients.

Methodology: Between December 2019 and March 2022, we carried out a cross-sectional investigation involving 191 patients diagnosed with type 2 diabetes. These patients were admitted to the internal medicine department at of the Public Hospital Establishment of "Ben Badis" and the Public Establishment of Local Health "Larbi Ben M'hidi Diabetes Centre" of Sidi-Bel-Abbes, Algeria. The criteria established by NCEP ATPIII (National Cholesterol Education Program Adult Treatment Panel III) were employed to define the presence of metabolic syndrome (MetS). Diagnosis of peripheral arterial disease (PAD) was based on Angiography and an ankle-brachial index (ABI) below 0.9.

Results: Of the 191 diabetic individuals, 47.1% had PAD and 78.5% had MetS; 52.66% of MetS patients developed PAD. Significant differences ($p<0.05$) in age, LDL, TG, CRP, serum chloride, and fibrinogen were noted between PAD and NPAD groups. Causal associations ($p<0.05$) were found between PAD and male gender, obesity, hypertension, dyslipidemia, inactivity, and MetS. PAD increased with MetS anomalies. Strongest PAD risks were low HDL, high TG, and blood sugar cluster (OR=10.75), followed by high waist circumference, TG, blood pressure, and blood sugar cluster (OR=8.361).

Conclusion: This study reveals a strong MetS-PAD association and highlights how specific MetS components independently influence PAD occurrence in adult type 2 diabetes patients.

Keywords: Peripheral Arterial Diseases; Metabolic Syndrome, Diabetes.

INTRODUCTION

Elevated blood sugar levels linked to diabetes, a prominent issue in public health, have detrimental effects on various physiological systems, notably impacting nerves and blood vessels. The prevalence of diabetes cases has risen dramatically in recent decades. In comparison to 108 million in 1980, the International Diabetes Federation (IDF) estimated that the global population of individuals residing with diabetes was approximately 537 million in 2021[1] and expected an increase to 700 million by the year 2045.[2]

Exhibiting odds ratios ranging from 2 to 4 based on population, diabetes stands alongside smoking as a prominent risk element for cardiovascular diseases (CVD), encompassing peripheral artery disease (PAD). All arteries, excluding the coronaries, are affected by PAD. It impacted more than 200 million people worldwide in 2010.[3] Diabetic patients experience PAD's rapid progression to critical limb ischemia, amputations and premature mortality.[4] The distinctive feature of diabetic vasculopathy involves the presence of extensive calcific plaques on both sides of arteries located beneath the knee. These plaques pose a formidable difficulty when attempting their extraction via angioplasty, resulting in ulcerations and sometimes in amputations.[4] Diabetes is viewed as a risk factor rather than as a separate domain.[5] Individuals who have both diabetes and PAD experience poorer quality of life, more perioperative complications, higher death rates, and higher costs healthcare,[6] moreover, Its occurrence is more pronounced among individuals with diabetes compared to those without the condition. Estimates indicate that peripheral artery disease (PAD) is prevalent in approximately 10 to 26% of the general population, while the range expands to 20 to 28% among individuals diagnosed with diabetes,[7,8] and this number can reach as high as 50% in cases of foot ulceration and more than 70% in those who have had lower limb amputations.[9] There have been major modifications in practice guidelines in recent years, according to studies, as a result

of research on the relationship between PAD and diabetes as a particular risk. These recommendations have started to take the recent rise in the incidence of this connection into consideration. These recommendations state that diabetics should get a PAD exam every year.[10]

A couple of risk factors for metabolic angiocardiopathy known as the metabolic syndrome include hypertension, obesity, atherogenic dyslipidemia, and diabetes.[11] Metabolic syndrome (MetS) demonstrates an autonomous connection with the risk of developing cardiovascular disease (CVD) and mortality. This risk escalates proportionally with the accumulation of MetS components.[12] MetS is projected to impact approximately one-quarter of the global population[13] as individuals diagnosed with diabetes constituting a substantial portion, approximately 70 to 80%, of MetS cases.[11]

The principal aim of this research was to evaluate the correlation existing between Metabolic Syndrome (MetS) and Peripheral Arterial Disease (PAD). Additionally, the study aimed to analyze the impact of individual constituents of MetS on the manifestation of PAD within the cohort of adult patients diagnosed with type 2 diabetes.

METHODOLOGY

Patients admitted to the internal medicine department of the Public Hospital Establishment of "Ben Badis" and the Public Establishment of Local Health “Larbi Ben M'hidi Diabetes Centre” of Sidi-Bel-Abbes, Algeria. from December 2019 to March 2022 were included in this study. Participants who were either non-diabetic or had diabetes along with cancer, severe cardiovascular disease (CVD), chronic kidney diseases, acute infections, autoimmune diseases, contagious diseases, HIV, HCV, or were pregnant were excluded from this investigation.

Essential information, including age, gender, smoking habits, alcohol consumption, familial history of diabetes, presence of hypertension, CVD, dyslipidemia, and comprehensive lifestyle details, was collected through in-person interviews conducted face-to-face (Figure 1).

Biochemical assessments, including glycated hemoglobin (HbA1c), high-density lipoprotein (HDLc), low-density lipoprotein (LDLc), total cholesterol (TC), triglycerides (TG), calcium levels, C-Reactive Protein (CRP), chloride, and fibrinogen, were performed using data from patients' medical records.

The Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in square meters (Kg/m²). Simultaneously, waist circumference was measured in centimeters at the umbilical level.

Blood pressure measurements were taken using a sphygmomanometer, with all participants in a seated position during the procedure. The primary recorded value for each measurement was the mean of two readings, with a 10-minute interval between repetitions.

Metabolic Syndrome (MetS) was defined based on the parameters outlined in the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria 14. The diagnostic criteria for peripheral arterial disease (PAD) included an ankle-brachial index (ABI) of less than 0.9, in conjunction with the utilization of angiography.

Simple random sampling without replacement was used, ensuring that each type 2 diabetic patient living in Sidi-Bel-Abbes had an equal opportunity to participate in the investigation.

The sample size was determined using the formula: $n0 = [Z^2 * P (1 - P)]/e^2$, where (Z) represents the confidence level (1.96 for a 95% confidence interval), (P) is the baseline indicator level (the true percentage of eligible patients), and (e) is the acceptable margin of error. Subsequently, the sample size was adjusted using: $n = n0 / [1 + (n0/N)]$, where (n0) is the initial sample size, (N) is the total population size, and (n) is the corrected sample size. With an estimated population of approximately 16,000 individuals with type 2 diabetes in Sidi-bel-Abbes city, the final sample size was approximately 191.

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) software, version 22.0 for Windows. The student t-test was employed to compare mean values between patients with and without PAD ($p<0.05$ considered statistically significant). The Chi-square test was used to examine causal relationships between PAD and factors such as male gender, obesity, hypertension, dyslipidemia, sedentarity, and MetS ($p<0.05$ considered statistically significant).

To assess the associations between PAD and the clustering of MetS components, Binary Logistic Regression analysis was utilized to calculate unadjusted and adjusted odds ratios (OR) (95% CI), allowing for an examination of PAD occurrence concerning the quantity and groupings of MetS constituents. Statistical significance was attributed to p-values below 0.05.

RESULTS

Upon a comprehensive analysis of 518 medical records, a rigorous selection process resulted in the inclusion of 191 subjects who precisely adhered to the defined sampling criteria. Table 1 summarizes the general features of the participants. Based on the presence or absence of PAD (PAD or NPAD), patients were categorized into two distinct groups. From the 191 diabetic

patients, 101 (52, 4 %) were male and 90 (47.1%) patients had PAD. The mean age was (60.54±15.22 years). According to Student t test, no statistically significant disparities ($p>0.05$) were observed between the two groups concerning Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), HbA1c, High-Density Lipoprotein (HDL), and Triglycerides (TG). However significant differences ($p \leq 0.05$) were highlighted (found) when comparing age, LDL, TG, CRP, serum chloride and fibrinogen levels with higher values in PAD group. The comparison of the two groups by the Chi-square test revealed causal relationships ($p \leq 0.05$) between male gender, obesity, hypertension, dyslipidemia, sedentarity, MetS and PAD. In relation to familial history of cardiovascular disease (CVD), hypertension, diabetes, and dyslipidemia, no statistically significant distinctions were identified between the PAD and NPAD groups (Table 1).

Out of the 191 individuals with diabetes, a substantial majority of 150 (78.5%) exhibited Metabolic Syndrome (MetS), with 79 (52.66%) of these MetS cases having progressed to Peripheral Arterial Disease (PAD). In contrast, 41 (21.5%) individuals without MetS experienced PAD, and within this group, 11 (26.82%) cases were identified as having developed PAD (Figure 2A). Figure 1B shows that the prevalence of PAD increased linearly with the number of MetS abnormalities in their respective groups; 2.5%, 9%, 23%, 30% and 32% (Figure 2B).

Binary logistic regression shows numerous positive relationships between PAD and various clusters of MetS components in diabetics (Table 2). Significant positive correlations were observed regarding cluster 1 ($p<0.001$), cluster 4 ($p =0.003$), cluster 6 ($p =0.019$) and cluster 7 ($p =0.008$). Regarding odd ratio, low HDL and high TG and blood sugar cluster (association between atherogenic dyslipidemia and diabetes) was the strongest risk factor of PAD followed by higher waist circumference, TG, blood pressure and blood sugar cluster (association between abdominal obesity, higher TG, hypertension and diabetes) with an odd ratio of 10.75 and 8.361, respectively (Table 2).

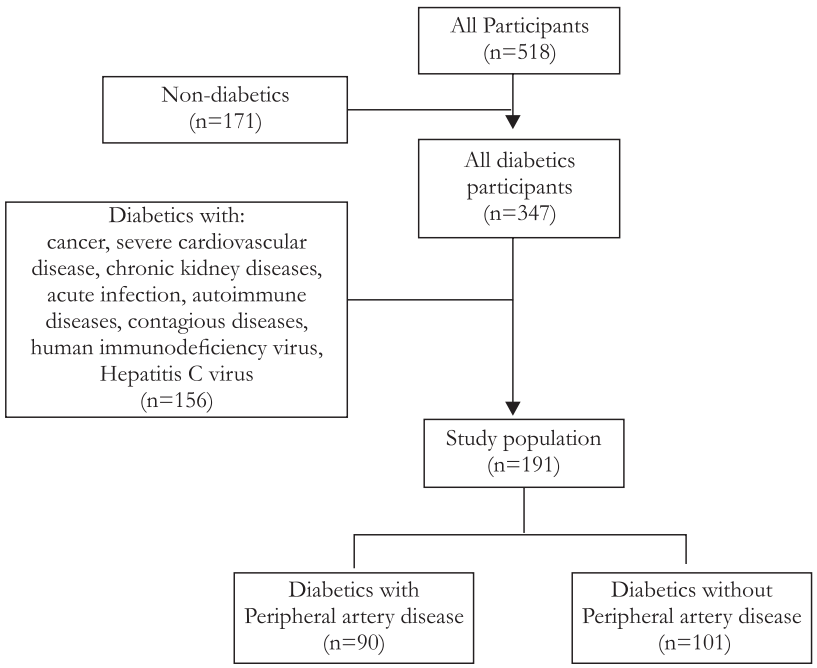

Figure 1: Flow chart of participants' selection.

DISCUSSION

The focal point of this research was to investigate the complex interconnection between Metabolic Syndrome (MetS) and its constituent elements, alongside the occurrence of Peripheral Arterial Disease (PAD), within a cohort of adult patients managing type 2 diabetes.

In the literature, the first comprehensive multicenter survey, encompassing over 10,000 subjects diagnosed with diabetes, examined the relationship with peripheral arterial disease (PAD) and documented a prevalence of diabetic PAD at 21.2%.[15] However, Gao et al. have reported a higher figure in elderly patients with diabetes (48.4%) which has paying attention of clinicians.[16] This result corroborates our findings (47.1%).

Patients with PAD exhibited slightly elevated metabolic indices compared to those without PAD, nonetheless, this difference was not significant[16] and others studies highlighted significant differences regarding systolic pressure only.[17,18] However, our results are different where most MetS abnormalities are higher in the PAD group comparing to those in the NPAD group (dyslipidemia, hypertension and obesity). Hypertension was the most observed component of MetS in PAD, followed by low HDL levels and hyperglyceridemia.[19] We found that the prevalence of hypertension was statistically higher in the PAD group ($p \leq 0.05$), associated with slightly higher TG levels and low HDL levels. Gorter et al. reported that MetS was highly prevalent in PAD patients with a rate of 58% (65% for women versus 55% for men). MetS patients had lower ABI, elevated CRP levels, increased BMI, high fasting glucose and high prevalence of previous myocardial infarction.[20] Comparative results were highlighted in our study, in which, prevalence of MetS in PAD subjects was (52, 66%) associated with high levels of HbA1c, CRP, fibrinogen and elevated BMI. Several studies reported similar

Table 1: Fundamental characteristics of the study cohort based on the presence of both peripheral arterial diseases and diabetes.

Parameters N (%)		Total 191 (100)	Type 2 diabetics without PAD 101 (52.9)	Type 2 diabetics with PAD 90 (47.1)	p value
Age (years); Mean ± S.D		60.54±15.22	57.58±16.98	63.75±14.28	<0.001*
Patients' gender; n (%)	Female	91(46.60)	58 (30.4)	33 (17.3)	0.003#
	Male	100(52.40)	43(22.5)	57 (29.8)	
Corpulence; n (%)	Normal weight 18.5≤BMI>25	46(30.30)	35 (23.00)	11 (07.20)	0.003#
	Overweight 25 ≤ BMI > 30	67(44.10)	43 (28.30)	24(15.80)	
	Obese BMI ≥ 30	39(25.80)	18(11.80)	21(13.80)	
Waist circumference; n (%)	< 102 for men < 88 for women	65(34.90)	34 (18.30)	31 (16.70)	0.549
	≥ 102 for men ≥ 88 for women	121 (65.1)	63 (33.90)	58 (31.20)	
Hypertension; n (%)	No	92(48.20)	64(33.50)	28(14.70)	0.017#
	Yes	99(51.80)	37(19.40)	62(32.50)	
Dyslipidemia; n (%)	No	98 (51.30)	77 (40.30)	21 (11.00)	<0.001#
	Yes	93 (48.70)	24 (12.60)	69 (36.10)	
Lifestyle; n (%)	Sedentary	106(57.00)	48 (25.40)	58(31.20)	0.033#
	Active	80(43.00)	48(25.80)	32 (17.20)	
Family history (CVD, Hypertension, Diabetes, Dyslipidemia); n (%)	No	19 (12.50)	26(38.20)	38 (19.90)	0.066#
	Yes	56(36.60)	66(43.40)	66(43.40)	
Metabolic syndrome	No	41(21.50)	30(15.70)	47(14.20)	0.003#
	Yes	150(78.50)	31(37.20)	79(41.40)	
SBP (cmHg); Mean ± S.D		12.31±02.06	11.87±01.95	12.77±02.08	0.646*
DBP (cmHg); Mean ± S.D		06.81±01.34	06.60±01.24	07.02±01.42	0.256*
HbA1c (%); Mean ± SD		08.62±02.17	08.51±01.53	08.74±02.31	0.564*
HDLc (g/l); Mean ± S.D		00.43±00.15	00.46±00.11	00.40±00.18	0.437*
LDLc (g/l); Mean ± S.D		01.07±00.41	01.07±00.39	01.07±00.49	<0.001*
TC (g/l); Mean ± S.D		01.66±00.48	01.65±00.39	01.69±00.56	<0.001*
TG (g/l); Mean ± S.D		01.36± 00.67	01.27±00.68	01.47±00.66	0.582*
Calcemia (mg/l); Mean ± S.D		90.50 ± 16.16	91.53±14.52	88.84±18.51	0.950
CRP(g/l); Mean ± S.D		26.24± 35.82	12.33 ± 13.50	47.87± 47.36	<0.001*
Cl (mmol/l); Mean ± S.D		94.32±16.23	93.37± 16.62	95.77 ±15.64	0,990
Fibrinogen (g/l); Mean ± S.D		05.49 ±04.90	03.97±03.47	07.71 ±05.79	<0.001*

(*) p value for student t test (#) p value for Chi-square test p ≤ 0.05 was considered as statistically significant. PAD peripheral arterial diseases, NPAD non peripheral arterial diseases, BMI body mass index, CVD cardio-vascular diseases, SBP systolic blood pressure, DBP diastolic blood pressure; HbA1c glycated hemoglobin, HDLc high-density lipoproteins, LDLc low-density lipoprotein, TC total cholesterol, TG triglyceride, CRP C-reactive protein, Cl blood chlorine.

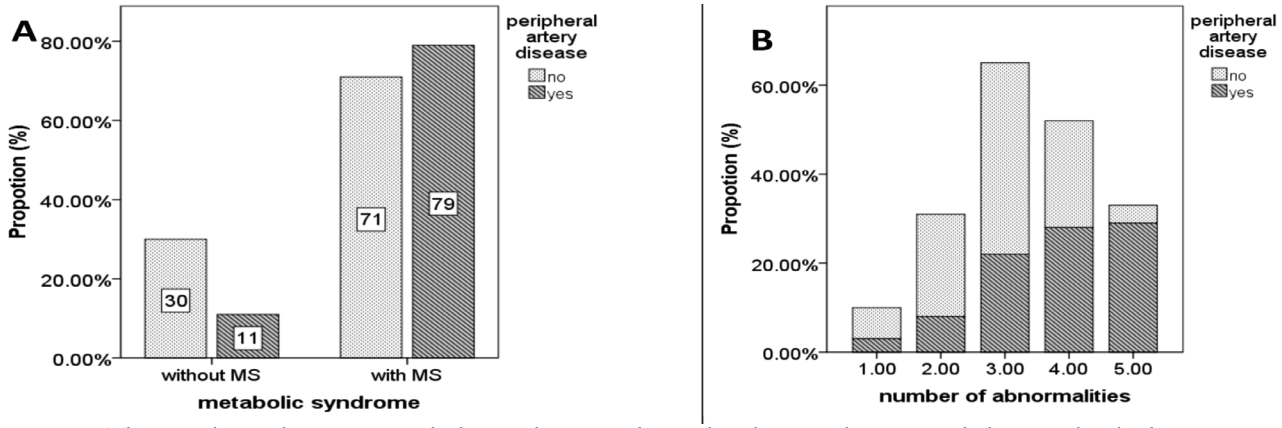

Figure 2A: The correlation between metabolic syndrome and peripheral artery diseases in diabetic individuals; 2B: Linear Increase of Peripheral Artery Disease Prevalence with Number of Metabolic Syndrome Abnormalities

Table 2: Crud "Odds Ratios" of metabolic syndrome components in relation to the presence or absence of peripheral arterial disease.

MetS components	n (%)	B	Odds ratio (95% CIOR)	P value
Cluster 1 WC, HDLc, TG, BP, BS	8 (4.18%)	-3.538	0.029 [00.008- 01.050]	<0.001
Cluster 2 HDL, TG, BP, BS	16 (8.37%)	1.181	3.258 [00.837- 12.680]	0.089
Cluster 3 WC, HDL, BP, BS	3 (1.57%)	1.276	3.583 [00.280- 45.796]	0.326
Cluster 4 WC, TG, BP, BS	13 (6.80%)	2.124	8.361 [02.093- 33.406]	0.003
Cluster 5 WC, HDL, BS	8 (4.18%)	0.024	1.024 [00.107- 09.838]	0.984
Cluster 6 HDL, TG, BS	31 (16.23)	2.375	10.75 [01.480- 78.064]	0.019
Cluster 7 WC, TG, BS	5 (2.61%)	1.510	4.526 [01.479- 13.857]	0.008
Cluster 8 WC, BP, BS	29 (15.18%)	0.181	2.389 [00.389- 14.656]	0.347

figure 60% and 57% in Olijhoek[21] and Brevetti[22] studies. Others studies reported very high percentage 97%[23] and low percentage (24%).[24] Despite this low percentage, the authors of this study suggested that MetS can predict to PAD development because only 15% of subjects without syndrome develop PAD vs 25 with MetS.[24]

Within our study, we observed a linear rise in the prevalence of peripheral arterial disease (PAD) corresponding to the increasing count of abnormal metabolic syndrome (MetS) components, so do the cases of PAD. Comparative results were highlighted by Gao et al., the presence of two or more components of Metabolic Syndrome (MetS) exacerbates vascular deterioration. With the aggregation of three or more MetS components, the susceptibility to peripheral arterial disease (PAD) notably surpassed that of individuals manifesting only one or two metabolic anomalies.[16,25]

According to Wilcox et al., obesity demonstrated the weakest association with peripheral arterial disease (PAD) compared to smoking, hypertension, hypercholesterolemia, and obesity.[26] Nevertheless, Akram et al. discovered inconsistent findings[27], their findings suggest a connection between obesity and increased waist circumference with peripheral vascular diseases (PVD), while observing no significant links between the duration of diabetes, smoking, and PVD. Others studies found that obesity, hypertension, diabetes and dyslipidemia are strong predictors of PAD.[28] We found that the cluster between HDL, TG and blood sugar, emerged as the most potent risk factor for peripheral arterial disease (PAD), obesity took precedence, succeeded by waist circumference, triglycerides (TG), blood pressure, and the aggregation of blood sugar. This cluster exhibited odds ratios of 10.75 and 8.361, respectively.

Our study faced some limitations. First, most participants are under antihypertensive medications, oral antidiabetics, insulin, and statins, which may affect the quality of our results. Second, the prevalence of the MetS varies between populations, therefore, the applicability of our findings to broader populations could be constrained. Third, the sample size was limited since the cases with incomplete medical records were excluded.

CONCLUSION

In conclusion, through this study, we not only established a significant association between MetS and PAD but also unraveled the distinct impact of each individual component of MetS regarding the manifestation of peripheral arterial disease (PAD) among adult individuals diagnosed with type 2 diabetes. This investigation shed light on the intricate interplay between these conditions, enhancing the understanding of pathophysiological processes that contribute to the emergence of peripheral arterial disease (PAD) within the context of type 2 diabetes. Our findings contribute valuable insights to both clinical practice and further research endeavors, underscoring the importance of addressing MetS components as potential contributors to the risk of PAD in this patient population.

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Author's Contribution

BI and MD conceived the idea, collected data, performed data analysis and data interpretation, write up of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

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