The relation of anatomical distribution of symptomatic peripheral arterial disease (PAD) with HbA1c level in patients with type 2 diabetes mellitus

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Abstract

Aims: Increased level of glycated hemoglobin (HbA1c) is associated with an increased prevalence of peripheral arterial disease (PAD). This study aimed to assess the relationship between the anatomical distribution of symptomatic PAD lesions in patients with type 2 diabetes and HbA1c levels at the time of PAD diagnosis.

Patients and methods: A retrospective study was conducted at King Abdullah University Hospital during the period August 2011 to December 2015. Consecutive patients with type 2 diabetes presented with symptomatic PAD confirmed by computed tomography-angiography (CTA) were included in this study. CTA images were reviewed. Relevant information including demographic data, PAD symptoms, comorbidities, HbA1c level, lipid profile, C-reactive protein and the mean platelets volume were retrieved from medical records.

Results: A total of 332 patients with type 2 diabetes (255 males and 77 females) were included in this study. The mean HbA1c at the time of PAD diagnosis was 8.68% (±2.06%). The prevalence of hemodynamic relevant atherosclerotic lesions of the superficial femoral artery, popliteal artery, leg vessels, femoro-popliteal, and crural segments was significantly higher in patients with HbA1c >7.5% compared with patients with HbA1c ⩽7.5%.

Conclusion: The anatomical distribution of symptomatic PAD in patients with type 2 diabetes mellitus differed significantly according to HbA1c level at the time of PAD diagnosis.

Keywords: diabetes mellitus, HbA1c, PAD distribution, peripheral arterial disease

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Introduction

Peripheral arterial disease (PAD) refers to occlusive arterial disease of the large and medium-sized arteries, except coronary and intracranial arteries.[1] Lower limbs PAD refers to occlusive atherosclerosis of at least one lower limb artery with ⩾50% reduction in diameter or total occlusion.[2] Prevalence of PAD in patients with type 2 diabetes is twice as common as that in non-diabetics and it is a strong predictor of subsequent cardiovascular morbidity and mortality.[3,4] Patients with type 2 diabetes are at an increased risk for coronary heart disease.[5] Duration of diabetes mellitus,

level of glycemic control and insulin resistance are associated with increased prevalence of PAD and other cardiovascular complications.[6]

Patients with type 2 diabetes and PAD have a high risk for limb loss.[7,8] Lower limb amputation rate is associated with increasing level of glycated hemoglobin (HbA1c).[8] Furthermore, patients with type 2 diabetes and PAD have poor outcome, which might be attributed to the associated cardiovascular co-morbidities and the extent, severity, and distal distribution of occlusive atherosclerotic lesions.[7,9] The incidence and severity of PAD

symptoms are associated with increasing levels of HbA1c in the adult diabetic population.[10] The relation of glycemic control with cardiovascular and all-cause mortality in patients with type 2 diabetes was explored by several investigators; the reported results were conflicting.[11–14]

To the best of our knowledge, the relation between the anatomical distribution of symptomatic PAD in patients with type 2 diabetes and HbA1c level has not been studied yet. Therefore, this study aimed to assess the relationship between the anatomical distribution of symptomatic PAD in patients with type 2 diabetes and HbA1c levels at the time of PAD diagnosis.

Patients and methods

This retrospective study included patients with type 2 diabetes aged >40 years, who presented with chronic symptoms of PAD in at least one lower limb confirmed by diagnostic computed tomography-angiography (CTA) (Multi-detector 128 slice, Philips, Ingunity, The Netherlands). The exclusion criteria included patients with lower limb peripheral vascular interventions prior to the study period (49 patients), major lower limb amputation prior to the study period (19 patients), acute lower limb ischemia (12 patients), trauma (five patients), poor quality CTA images (six patients), and CTA images with no hemodynamic relevant atherosclerotic lesion (HRAL) in four patients. All patients were managed at King Abdulla University Hospital (KAUH) between August 2011 and January 2015.

The Institutional Review Board of Jordan University of Science and Technology approved this study (26/108/2017) and waived the need for informed consent. Patients were considered to have type 2 diabetes if their medical records documented the diagnosis of type 2 diabetes. Patients were considered symptomatic if they had intermittent claudication, pain at rest, and tissue loss (ulceration or gangrene). Abdominal aorta and lower extremity CTA with distal runoff were used as the diagnostic modalities for patients with type 2 diabetes presenting with symptoms suggestive of PAD and abnormal ankle–brachial pressure index (<0.9 or ≥1.4). Two interventional vascular radiologists reviewed and scored the CTA images. The final approved reports were archived in the radiology database.

The senior interventional vascular radiologists reviewed CTA images with no knowledge of patients' clinical and laboratory data. Lower limb arterial tree from the abdominal aorta just distal to the renal arteries down to the ankle was reported for the presence of HRAL in individual arteries of both lower limbs. HRALs of both lower limb arteries, symptomatic, and asymptomatic limbs were included.

HRAL was defined as ≥50% reduction in the diameter or complete occlusion of an individual artery, whether single, multiple, short, or long lesions. An individual artery with HRAL was considered diseased. The arterial tree of each limb was divided into three segments: the aorto-iliac (AI), femoro-popliteal (FP), and crural segments. The AI segment includes the infra-renal abdominal aorta, the common iliac artery, and the external iliac artery up to the level of the inferior epigastric artery. The FP segment included the common femoral, deep femoral, superficial femoral (SFA), and popliteal (PA) arteries up to the anterior tibial artery (ATA) takeoff. The crural segment included the ATA, posterior tibial (PTA), and peroneal arteries up to the level of the ankle.[15] Arterial segment was considered diseased if at least one of its component arteries was involved with at least one HRAL.

The hospital database was used for extracting the relevant information including the demographic characteristics (age and sex), clinical presentation (intermittent claudication, pain at rest, foot ulcers, and gangrene), history of smoking, associated health problems (hypertension and ischemic cardiac disease), and laboratory data at the time of PAD diagnosis. For laboratory investigations, blood samples were obtained from patients after 12h of fasting. HbA1c was determined by hemchromatography of whole blood sample using automated hematology analyzer Cobas c 501 (Roche, Germany). The lipid profile was determined by spectrophometry method of serum sample using fully automated computerized chemistry analyzer Cobas c501 (Roche, Germany). Low-density lipoprotein (LDL) cholesterol was calculated from the values of high-density lipoprotein (HDL) cholesterol, triglycerides and total cholesterol by using the Fried–Ewald formula. Mean platelet volume (MPV) was measured by the electrical impedance method of whole blood sample using Beckman Coulter DXH 800 (USA). C-reactive protein

(CRP) was measured by spectrophotometry of serum sample using Cobas 501 (Roche, Germany). All laboratory measurements were retrieved from the laboratory database. The values of these laboratory variables at the time of diagnostic CTA (within 4 weeks) were used for data analysis and comparison. Patients were categorized into two groups according to the level of HbA1c: HbA1c ≤ 7.5% and HbA1c > 7.5%.[10,16–18]

Sample size was calculated at a power of 80% and a level of significance of 0.05. Assuming that 60% of patients with type 2 diabetes who underwent diagnostic CTA had HbA1c > 7.5%, the sample size needed to detect an odds ratio of 2 between diseased arteries and HbA1c was calculated to be 302 patients.

IBM SPSS Statistics for Windows, version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. IBM Corp., Armonk, NY, USA) was used for data analysis. Categorical variables were described using percentages and continuous variables were described using means and standard deviations. The distributions of laboratory parameters were checked graphically for normality using histograms. All laboratory parameters were approximately normally distributed. The arterial and segmental involvement with HRAL in the patients with HbA1c > 7.5% was compared with that in the patients with HbA1c ≤ 7.5%. Unpaired Student's *t*-test was used to compare the means, and the chi-square test was used to compare the proportions. A separate binary logistic regression model was used to test the significance of the differences in each diseased artery/segment between patients with HbA1c > 7.5% and those with HbA1c ≤ 7.5%. A *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 427 patients with type 2 diabetes aged > 40 years had diagnostic CTA. Of those, 332 patients [255 men (76.8%) and 77 women (23.2%)] with type 2 diabetes fulfilled the inclusion criteria. Their mean age (±SD) was 63.6 (±10.5) years; 62.5 (±10.6) years for men and 67.1 (±10.5) years for women (*p* < 0.05). The mean age of patients with HbA1c ≤ 7.5% was 62.8 (±10.4) years and the mean age was 64.0 (±10.5) years for patients with HbA1c > 7.5%. The mean HbA1c for all patients was 8.7%

(±2.1%), 8.6% (±3.5%) for males and 9.1% (±3.4%) for females (*p* = 0.004). The young age group (≤ 60 years) constituted 47% of patients with type 2 diabetes presenting with symptomatic PAD. The mean HbA1c in the young age group was 8.6% (±2.09%) compared with 8.8% (±2.04%) in patients aged > 60 years (*p* = 0.131).

The demographic and clinical characteristics according to the HbA1c level are shown in Table 1. The results of laboratory investigations (total cholesterol, triglyceride level, LDL, HDL CRP, MPV) of the patients according to the HbA1c level at the time of PAD diagnosis are presented in Table 2.

Of the 664 limbs in 332 patients with type 2 diabetes, 304 (45.8%) were asymptomatic limbs while 360 (54.2%) were symptomatic limbs. The mean HbA1c for patients with asymptomatic limbs was 8.69% (±2.07%) compared with 8.7% (±2.07%) in patients with symptomatic limbs (*p* = 0.974). The prevalence of smoking was not significantly different between patients with HbA1c level > 7.5% and those with HbA1c ≤ 7.5% (*p* = 0.088).

The distribution of HRAL was ATA (39%), SFA (38%), and PTA (36%). Figure 1 shows the distribution of arterial HRAL according to the HbA1c level at the time of PAD diagnosis. Of all arteries, SFA, PA, ATA, PTA, and the peroneal artery were significantly more likely to be diseased in patients with HbA1c > 7.5.

HRALs were seen in 52% of the FP segments, and 49.9% of the crural segments. Isolated FP involvement with HRAL was seen in 19.6%, and isolated crural involvement was seen in 17.9% of the limbs. Concomitant FP and crural involvement with HRAL were seen in 20.2% of the limbs. In contrast, isolated AI involvement with HRAL was seen in 13.2% of the patients. Concomitant AI and FP involvement was seen in 5.4%, AI and crural involvement was found in 5%, and concomitant involvement of all segments was seen in 6.8% of the limbs. Only 11.9% of the limb segments were free of HRAL.

Table 3 shows the distribution of segmental HRALs in relation to HbA1c levels. FP and crural segments were significantly more likely to be diseased in the limbs of patients with HbA1 > 7.5%, compared with patients with HbA1c ≤ 7.5%.

Table 1. Demographic and clinical characteristics of the patients in relation to HbA1c level at the time of symptomatic peripheral artery disease diagnosis.

Characteristics for 332 patients	HbA1c level		Total n (%)	p-value
	≤7.5% n (%)	>7.5% n (%)		
Age, years				
≤60	74 (42.9)	89 (57.1)	156 (47.0)	0.004*
>60	56 (31.8)	120 (68.2)	176 (53.0)	
Gender				
Male	103 (40.4)	152 (59.6)	225 (76.8)	0.001*
Female	20 (26.0)	57 (74.6)	77 (23.2)	
Smoking				
No	52 (41.3)	74 (58.7)	126 (38.0)	0.088
Yes	71 (34.5)	135 (65.5)	206 (62.0)	
Hypertension				
No	49 (38.0)	80 (62.0)	129 (38.9)	0.740
Yes	74 (36.5)	129 (63.5)	203 (61.1)	
Cardiac disease				
No	80 (38.8)	126 (61.2)	206 (62.0)	0.247
Yes	43 (34.1)	84 (65.9)	126 (38.0)	
Symptoms for 664 limbs				
No	113 (37.2)	191 (62.8)	304 (45.8)	0.009*
Yes				
Intermittent claudication	65 (51.6)	61 (48.4)	126 (19.0)	
Rest pain	10 (37.0)	17 (63.0)	27 (4.1)	
Ulcer	41 (30.8)	92 (69.2)	74 (20.0)	
Gangrene	17 (23.0)	57 (77.0)	74 (11.1)	

*Statistically significant, chi-square test was used to compare percentages.
HbA1c, glycated hemoglobin.

HRALs of the proximal arteries and AI segments did not differ significantly between the patients according to their HbA1c levels.

Table 4 shows the multivariate analysis of the differences in the segmental and arterial involvement with HRAL between patients with HbA1c >7.5% and patients with HbA1c ≤7.5%, after adjusting for sex and age. The FP and crural segments were significantly more likely to be diseased in the limbs of patients with HbA1c >7.5%, compared with those in patients with HbA1c ≤7.5%. Similarly, the odds ratio of having diseased SFA, PA, ATA, PTA, and peroneal artery were significantly higher in patients with HbA1c >7.5%.

Table 2. The laboratory characteristics of patients based on HbA1c levels.

Variable	HbA1c		*p*-value
	≤7.5%	>7.5%	
	Mean ± SD	Mean ± SD	
Total cholesterol, mmol/L	4.8 ± 1.3	4.6 ± 1.0	0.015*
Triglyceride level, mmol/L	2.5 ± 1.5	2.2 ± 1.4	0.006*
LDL mmol/L	3.1 ± 1.0	3.0 ± 0.8	0.013*
HDL, mmol/L	0.9 ± 0.3	1.0 ± 0.3	0.017*
C-reactive protein, IU/L	53.3 ± 56.0	66.4 ± 54.8	0.003*
Mean platelets volume, fL	9.7 ± 1.1	9.8 ± 1.3	0.415

*Statistically significant. Independent *t*-test was used to compare means.
HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
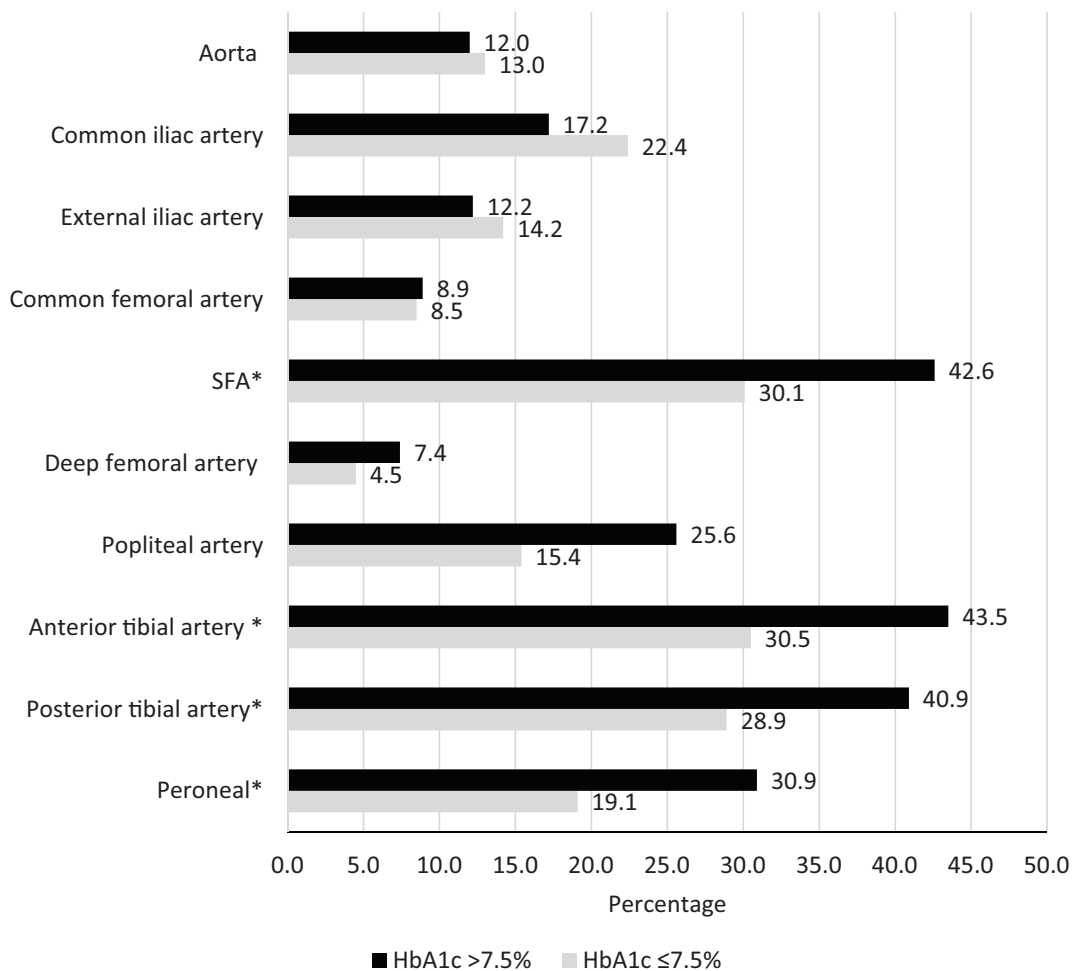
Figure 1. The distribution of diseased arteries according to HbA1c.
*Statistically significant difference according to the HbA1c level.
HbA1c, glycated hemoglobin; SFA, superficial femoral artery.

Table 3. The distribution of diseased segments according to HbA1c level at the time of peripheral arterial disease diagnosis.

Segment	HbA1c level		p-value
	≤7.5%	>7.5%	
	n (%)*	n (%)*	
Aorto-iliac segments	82 (33.3)	123 (29.4)	0.293
Femoro-popliteal segments	114 (46.3)	235 (56.2)	0.014**
Crural segments	108 (43.9)	232 (55.5)	0.004**

*n refers to number of diseased segments.
**Statistically significant, chi-square test was used to compare percentages.
HbA1c, glycated hemoglobin.

Table 4. Multivariate analysis of the differences in the diseased arteries between patients with HbA1c >7.5% and patients with HbA1c ≤7.5% (HbA1c >7.5% *versus* ≤7.5%) after adjustment for gender and age.

	OR	95% confidence interval		p-value
Segment				
Aorto-iliac segment	0.9	0.6	1.2	0.430
Femoro-popliteal segment	1.4	1.0	2.0	0.033*
Crural segment	1.6	1.2	2.2	0.004*
Artery				
Aorta	0.9	0.5	1.4	0.575
Common iliac artery	0.8	0.5	1.2	0.211
External iliac artery	0.8	0.5	1.3	0.391
Common femoral artery	1.0	0.6	1.8	0.977
Superficial femoral artery	1.7	1.2	2.3	0.003*
Deep femoral artery	1.6	0.8	3.2	0.227
Popliteal artery	1.8	1.2	2.8	0.006*
Anterior tibial artery	1.8	1.3	2.6	<0.001*
Posterior tibial artery	1.6	1.2	2.3	0.005*
Peroneal artery	1.8	1.2	2.7	0.002*

*Statistically significant. Separate logistic regression model was developed for each segment/artery after adjusting for gender and age.
HbA1c, glycated hemoglobin; OR, odds ratio.

Discussion

Diabetes mellitus is a systemic complex metabolic disorder, characterized by chronic hyperglycemia, derangement of lipid metabolism, and insulin insufficiency. The severity and the duration of diabetes are associated with the pathophysiological mechanism of atherosclerosis.[19,20] Chronic hyperglycemia is associated with activation of oxidative

stress and over production of mitochondrial free oxygen species, resulting in reduction of endothelial nitric oxide and accumulation of advanced glycation products. Mechanisms for atherosclerosis include endothelial and vascular smooth muscle cell derangement and platelets activation that promote slow inflammatory process and thrombosis.[21,22] Several inflammatory markers are found in patient with diabetes, such as CRP, that are associated with PAD development and abnormal glucose metabolism.[23] Platelets are essential in the process of inflammation and thrombus formation.[24] Our results suggest a statistically significant correlation between HbA1c level and biochemical parameters (hyperlipidemia, CRP, and MPV); further investigations are needed to investigate their impact on anatomical distribution of atherosclerosis.

In this study, the male-to-female ratio was 3.3:1. Female patients were older and had poorer glycemic control at the time of diagnosis of symptomatic PAD compared with men. Our results were consistent with previous reports that showed male predominance in cases with symptomatic PAD.[15,25,26] In other studies, female patients were found to have poor glycemic control at the time of diagnosis and were less likely to undergo revascularization procedures.[19–27] However, recent studies demonstrated a comparable prevalence of asymptomatic PAD in both sexes.[28,29]

In this study, 47% of symptomatic limbs were seen in patients aged ≤60 years. Atherosclerosis is part of the aging process. PAD might have started a long time before it became symptomatic, even before the diagnosis of diabetes.[30] It has been reported that type 2 diabetes and atherosclerosis have the same pathological process.[31] The prevalence of PAD increases with age and affects approximately 20% of the population above 75 years of age.[31] Young male patients with diabetes tend to have severe PAD with a higher tendency for involvement of the proximal arteries;[15,26] a high proportion of young patients might partially explain the higher prevalence of AI segment involvement in this study.

HbA1c is a measure of long-term glycemic control and is used to monitor and guide the clinical treatment in individuals with diabetes.[32] Chronic hyperglycemia in patients with type 2 diabetes as measured by HbA1c can accelerate the atherosclerotic disease process, leading to ischemic macro-vascular events, including symptomatic PAD.[10,20] However, whether HbA1c is independently associated with the progression of atherosclerosis and cardiovascular events in individuals with diabetes remains controversial.[33] In a recent report, Arya *et al.*[34] found a significant increase in the rate of amputation and modified major adverse limb events with increasing levels of HbA1c in the pre-procedural period. The interaction between several risk factors is reported to enhance the acceleration and selectivity at different vascular beds and different segments of the same vascular bed.[35]

In most reported series, patients with type 2 diabetes had severe multi-segmental PAD disease with distal anatomical distribution.[6,36–39] Diehm *et al.*[26] found that infra-geniculate disease was associated with higher age, male sex, and diabetes mellitus. The multi-segmental and distal distribution of symptomatic PAD in patients with type 2 diabetes was demonstrated in this study. The HRALS in the AI segments were not significantly related to the HbA1c level. In contrast, HRALS in the distal segments (FP and crural) and their component arteries (SFA, PA, PTA, ATA, and peroneal artery) were significantly associated with HbA1c levels. The distribution of HRAL in different segments in this study is difficult to compare with the results of other studies because of the differences in the definition of the segments and the differences in the sample of the studies.[15,26,36,37]

The results of this study suggested that HbA1c above 7.5% in patients with type 2 diabetes was associated with a particular pattern of anatomical distribution of PAD. This association was particularly significant for the HRALs in the crural and FP segments.

The positive effect of glycemic control in reducing the prevalence of PAD in patients with type 2 diabetes was highlighted by the result of the UKPDS study, where an increase of 1% in HbA1c level was associated with a 28% increase in the risk of developing PAD.[40]

However, other studies demonstrated no significant benefit of intense glycemic control on macro vascular complications in type 2 diabetes mellitus.[41,42]

There is no consensus on the appropriate HbA1c level that represents desirable glycemic control. The American Diabetic Association recommends

a level of 7%.[43] Lebovitz suggested a level of 7.5%, especially in the fragile elderly with long-standing diabetes.[18] Arya *et al.*[34] reported poor outcomes of revascularization in patients with pre-procedural HbA1c >8%. Cumulative evidence supports that a HbA1c level of >7.5% is associated with poor outcomes and disease progression,[34] contrary to the results of the earlier studies about intense glycemic control.[44]

Implementing the results of this study can encourage further prospective studies to explore the benefit of achieving diabetic control that can avoid the risk of hypoglycemia due to intense glycemic control.

This study has some limitations. The study did not consider the nature of HRAL, such as multiple, single, long, short, stenosis, or occlusion. It is important to mention that only one reading of HbA1c was correlated with the anatomical distribution of PAD. HbA1c is highly variable throughout the year, and the one-time value does not reflect the control or the lack of control of the disease in general. A prospective study is essential to elucidate this association.

Conclusion
The anatomical distribution of the symptomatic PAD in patients with type 2 diabetes varied significantly according to the HbA1c level at the time of PAD diagnosis.

Author contributions
All authors have participated in research idea, data interpretation, analysis, writing and revisions which provided critical feedback, helped shape the research, and contributed to the final manuscript.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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