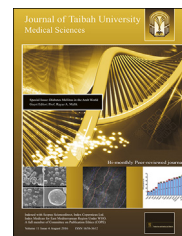




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Review Article

The prevalence and management strategies for peripheral artery disease associated with diabetes mellitus in the Arab world



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المخلص

هناك عدد متزايد من التقارير البحثية المنشورة عن داء السكري، الذي يعتبر مشكلة صحية عالمية، كما أن هناك تصاعدا مدهلا في انتشار داء السكري، وما يرتبط به من مضاعفات في جميع أنحاء العالم. ويعتبر مرض الشرايين الطرفية من المضاعفات المدمرة على المدى الطويل. وعلى الرغم من وجود زيادة هائلة في انتشار داء السكري في العالم العربي، إلا أن هناك تقارير قليلة تحتوي على بيانات ضعيفة لا تعكس الحجم الحقيقي للتحديات التي تواجهها مؤسسات الرعاية الصحية. تشمل عوامل الخطورة الرئيسية لأمراض الشرايين الطرفية التدخين، وداء السكري من النوع الثاني، وارتفاع ضغط الدم الشرياني، وارتفاع الدهون بالدم، وارتفاع الهوموسيستين في الدم، والتقدم في العمر. كما ترتبط أمراض الشرايين الطرفية بالعمر وغالبا ما يضعف تشخيصها، وتوقعها، وعلاجها بكفاءة. ويمثل تشخيص أمراض الشرايين الطرفية لمرضى السكري تحديا طبيا، فعلى الرغم من وجود فقدان شديد للأنسجة، إلا أن المريض قد يظل بدون أعراض بسبب اعتلال الأعصاب الطرفية. كما يعتبر وجود أمراض الشرايين الطرفية مؤشرا قويا لأمراض القلب والأوعية الدموية في المستقبل. والغرض من هذه المراجعة البحثية هو توفير بيانات حول داء السكري وانتشار أمراض الشرايين الطرفية الناتجة عن السكري مع تركيز خاص على دول العالم العربي. كما تضمنت المراجعة نظرة عميقة حول طرائق التشخيص، والمبادئ التوجيهية للعلاج. ومن الملاحظ أن هناك ارتفاعا كبيرا في انتشار أمراض الشرايين الطرفية الناجمة عن داء السكري، الأمر الذي يؤدي بدوره إلى اعتلال كبير في الصحة وانخفاض ملحوظ في نوعية الحياة. إن التعرف المبكر على الأشخاص الذين يعانون من عوامل الخطورة، يمكن أن يساعد في تقليل ظهور أمراض الشرايين الطرفية عند المرضى الذين يعانون من النوع الثاني من السكري، وبالتالي منع أمراض الأطراف والمضاعفات التي تهدد الحياة. ويقترح الباحثون إنشاء مركز بيانات على مستوى الوطن العربي حول تأثير داء السكري على أمراض الشرايين الطرفية.

الكلمات المفتاحية: داء السكري؛ مرض الشرايين الطرفية؛ انخفاض التروية بالأطراف؛ الفرغينية؛ مؤشر الضغط العضدي الكاحلي

Abstract

A growing body of published literature has indicated that diabetes mellitus (DM) is a global health epidemic. There is a staggering upsurge of the prevalence of DM and its associated complications across the globe. Peripheral artery disease (PAD) is a devastating long-term complication of DM. Although there is an exponential increase in the prevalence of diabetes in the Arab world, there are few reports that contain scant data that do not reflect the real magnitude of challenges to health-care agencies. Major risk factors for PAD include smoking, type 2 DM (T2DM), hypertension, hyperlipidaemia, hyperhomocysteinaemia, and advancing age. PAD is an age-dependent disorder that is under-diagnosed, under-estimated, and sub-optimally treated. Diagnosing PAD is challenging in patients with DM because, despite the presence of severe tissue loss, it may remain asymptomatic because of associated neuropathy. PAD is considered to be a strong predictor of future cardiovascular events. The purpose of this review is to provide data regarding the existing prevalence of DM and diabetes-induced PAD with special focus on the Arab world. Subsequently, deep insight regarding the diagnostic modalities and management guidelines is provided. There is a dramatic rise in the prevalence of diabetes-induced PAD that leads to significant morbidity and a marked reduction in the quality of life. Early identification of individuals with risk factors can help to minimize the onset of PAD in patients with DM, thus preventing limb and life-threatening complications. This review argues for more nationally representative surveillance data in the Arab world regarding the impact of DM on PAD.

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Keywords: Ankle brachial pressure index; Diabetes mellitus; Gangrene; Lower limb ischaemia; Peripheral artery disease

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Introduction

Diabetes mellitus (DM) is a major health challenge that explains a significant contribution to morbidity and premature mortality worldwide.¹ The projected number of global diabetic patients is estimated to rise from 135 million in 1995 to 300 million in 2025.² The number of people with undiagnosed T2DM is rapidly increasing, and there is a proportionately increased risk of developing complications in this group, many of whom have unidentified disease.³

In congruence with the global prevalence of DM, the Asia Pacific region is considered to be on the brink of an epidemic of DM.⁴ Several studies have reported a high prevalence of DM in various countries of the Middle East region such as Bahrain (25.7%),⁵ the KSA (23.7%),⁶ the Al Ain region of the United Arab Emirates (17.1%),⁷ and Jordan (16.9%).⁸ DM is a growing health problem in the Middle East region including KSA.⁹ In 1982, Bacchus RA published the first estimated prevalence of 2.5% of DM in KSA.¹⁰ This report showed that the prevalence of DM begins to rise at 35 years with a peak at 45–54 years. In 1987, Fatani et al. reported a prevalence of 4.3% in the rural areas,¹¹ followed by a subsequently reported prevalence of 9.7% by El-Hazmi MA et al., in 1996.¹² Another survey showed that “the age adjusted prevalence of DM was significantly higher in urban populations (males 12%, 95% CI = 11–13 and females 14%, 95% CI = 13–15) than in rural populations (males 7%, 95% CI = 7–8 and females 7.7%, 95% CI = 7–9), which is among the highest in the world”.¹³ Later, in 2004, Nozha et al. showed an estimated prevalence of DM in KSA of 23.7%.⁶ A changing lifestyle,¹⁴ increased longevity,^{15,16} lack of physical activity,¹⁷ change in dietary habits, and increasing urbanization¹⁸ are major reasons for this upsurge in the prevalence of DM in KSA in particular and in the Middle East in general.

A survey-based research study was conducted on the adult Qatari population to explore the prevalence of diagnosed and undiagnosed diabetes and pre-diabetes and to determine the associated risk factors of DM.¹⁶ “The identified risk factors were significantly higher in the diabetic adult Qatari population: central obesity ($p < 0.001$), hypertension ($p < 0.001$), triglyceride ($p < 0.001$), high-density lipoprotein ($p = 0.003$), metabolic syndrome ($p < 0.001$), heart diseases ($p < 0.001$)”.¹⁶ According to the International Diabetes Federation Report published in 2014, KSA was ranked 4th among the top five Middle Eastern and North African countries, with 3.6 million diabetics in the adjusted age group ranging from 20 to 79 years.¹⁹ T2DM affects nearly all systems of the body, which leads to a range of complex and chronic illnesses

such as diabetic nephropathy,²⁰ diabetic peripheral neuropathy (DPN),²¹ otopathy,²² PAD,²³ retinopathy,²⁴ coronary artery disease,²⁵ diabetic foot and trophic ulcers,²⁶ gallstones²⁷ and colorectal malignancy.^{28–30}

The rising prevalence of DM and its associated complications, particularly PAD, poses a great burden to the health care system.^{31,32} PAD refers to the atherosclerotic narrowing of the abdominal aorta, iliac and lower extremity arteries, presenting varying degrees of ischaemia, leading to intermittent claudication (IC), ulceration, gangrene or limb loss.³³ Therefore, from a community health perspective, it is imperative to identify the pathogenesis and management strategies of DM-induced PAD.³⁴ There are very few publications regarding DM and PAD in the Arab world. This review’s objective is to provide a comprehensive critique of the current published literature with a focus on comparing the current situation in the Arab world with the rest of the world. The existing deficiencies and gaps in the literature are identified, and future directions and challenges for research are outlined.

Search design

A literature search was conducted through the MEDLINE, EBSCO CINAHL, and ISI Web of Knowledge databases for English language articles by connecting MeSH terms “Diabetes mellitus” AND “Diabetic foot ulcers” AND “Arab world” OR “Peripheral arterial disease” in Endnote X 7, which retrieved 1742 citations. The further selection and exclusion of studies is outlined in Figure 1.

The burden of peripheral vascular disease

More than 202 million people have PAD worldwide, with approximately 70% residing in low-to middle-income countries.³⁵ There is an estimated increase of 3–7% in the prevalence of PAD that is positively correlated with advancing age.³⁶ “Although it was believed that the prevalence of PAD is common in men, the prevalence of PAD in women is at least equal, if not higher”.³⁷ Approximately 100,000 people are diagnosed annually with PAD in the UK and carry high chances of developing cardiovascular complications.³⁸ From the Arabian perspective, Alsheikh et al. conducted a cross-sectional study on all respective 45-year and older Saudi patients, who attended the primary health care centre at King Khalid University Hospital Riyadh.³⁹ Of 471 patients, the prevalence of PAD was 11.7% (95% CI: 8.9–14.9%), and 92.7% were asymptomatic. Patients with PAD were identified to have a range of risk factors including T2DM, hypertension, hyperlipidaemia, smoking, cerebrovascular accidents, and coronary artery disease. Another study conducted a 1-year follow-up study to determine the incidence of foot disorders such as PAD, DPN, foot ulcer, gangrene, and amputation, among 556 Saudi diabetic patients.⁴⁰ The 1-year cumulative incidence of PAD, peripheral neuropathy, foot ulcer, and gangrene was reported to be 6.3, 9.2, 3.6, and 16.7%, respectively.

The diabetic foot, resulting from either PAD or diabetic peripheral neuropathy, represents 1 in 5 hospitalizations among diabetics.⁴¹ The treatment costs of these foot

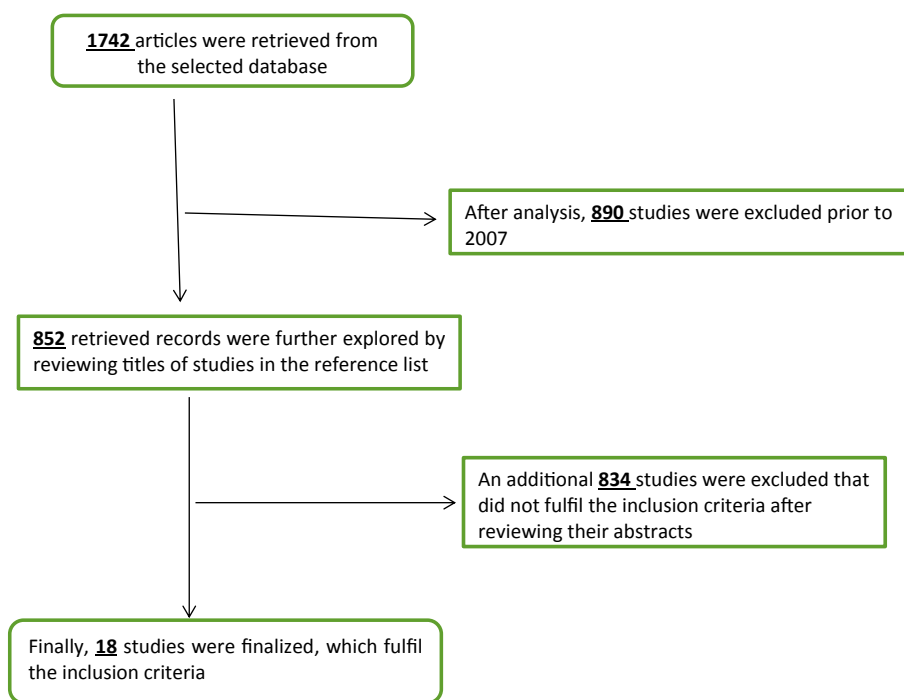


Figure 1: Flow diagram showing the search design for the selection of publications regarding diabetes mellitus and peripheral vascular disease in the Arab world.

complications consume approximately 25% of the hospital costs of total diabetes care.⁴² This finding places a huge burden on the financial and administrative resources of health-care sectors across the globe. Wang et al., in their cross-sectional study, explored the prevalence and correlates of lower extremity amputation in the Saudi population with diabetic foot ulcers due to PAD and DPN.⁴³ From a group of 91 participants, the investigators found a 29.7% prevalence of lower extremity amputation. The odds ratio for amputation was 2.42 (95% confidence interval [CI] = 0.70–8.45; p for trend = 0.03) for ulcer size and 0.22 (95% CI = 0.06–0.87; p for trend = 0.03) for high-density lipoprotein cholesterol. The overall prevalence of lower limb amputation in this study was found to be significantly higher than the previously reported data.

Diabetes mellitus as a leading risk factor for peripheral artery disease

Smoking, T2DM, hypertension, hyperlipidaemia, hyperhomocysteinaemia, and advancing age are the major risk factors for PAD.^{44–46} Obesity is another leading risk factor for T2DM as well as PAD.³² Positive correlations have been reported between obesity and DM in Iraq,⁴⁷ United Arab Emirates,⁴⁸ Egypt,⁴⁹ Jordan,⁵⁰ and Iran.⁵¹ The estimated risk in the diabetic patients of developing PAD is two to four times higher, and the risk of amputation is 15 times greater than in the non-diabetic population.⁵² Unfortunately, after amputation, the patients' mortality rate remains as high as 50% at 2 years. Longer diabetes duration, insulin use, and low haemoglobin levels have been reported to be associated with a higher prevalence of diabetic foot complications.⁵³ Both PAD and neuropathy

increase the risk of foot complications 10-fold compared with the non-diabetic population. In contrast, a prospective cohort study could not find a significant correlation between the duration of DM and the development of foot complications.⁴⁴

Alzahrani et al. investigated the correlation between risk factors and the prevalence of PAD in 598 Saudi diabetic patients.⁵⁴ This study reported PAD prevalence of 23.1%. “Hypertension (OR (odds ratio) = 2.13, 95% CI: 1.29–3.52), obesity (OR = 1.75, 95% CI: 1.13–2.73) and longer duration of diabetes (OR for ≥ 20 years vs 2–4 years = 3.30, 95% CI: 1.66–6.58) were independently and significantly associated with a higher prevalence of PAD”. This study reported a higher prevalence of DM-induced PAD than the published range of 20–30%.^{33,55} These findings emphasize the importance of identifying individuals with significant risk factors in an attempt to prevent the onset of PAD among patients with diabetes in KSA.⁵⁶

Diagnostic modalities for peripheral artery disease

The cardinal features of lower limb ischaemia are IC, resting pain, and gangrene. The initial presentation of PAD is IC,⁵⁷ and the symptoms of IC remain unchanged in the majority of people. When patients seek medical consultation, physicians often struggle to differentiate claudication from other common conditions such as hip arthritis and spinal stenosis. As many as 20% of patients will develop a progressive disease with more severe symptoms that leads to critical limb ischaemia.³⁶ The strategies commonly employed to diagnose PAD include a detailed medical history, physical examination, and

diagnostic tests. Undoubtedly, the most accurate clinical examinations for diagnosing PAD are unilateral absent or abnormal pedal pulses, changes in colour, cold foot, and bruit in the femoral artery.⁵⁸ Traditionally, the clinical staging for grading the severity of PAD is categorized according to the Fontaine or Rutherford classification, as shown in Table 1.⁵⁹ The non-invasive tools to confirm PAD include the ankle brachial pressure index (ABPI), pulse volume recording, Doppler flowmetry, and Doppler ultrasound. A treadmill test can provide an objective measure of walking capacity.^{60,61} The values of ABPI can determine the severity of lower limb ischaemia. A brief clinical interpretation of ABPI is outlined in Table 2.⁶²

Colour scanning combines B mode ultrasound with Doppler scanning to locate the narrowed segment in addition to evaluation of the size of the blockage.⁶³ Digital subtraction angiography (DSA), computerised tomography angiogram (CTA), and magnetic resonance angiogram (MRA) can provide comprehensive information regarding the location and size of obstruction as well as the architectural details of the arterial skeleton.⁶⁴ CTA and MRA are usually reserved for those who are being considered for angioplasty or arterial reconstruction surgery.⁶⁵

Management of peripheral artery disease and diabetes mellitus

The International Working Group on the Diabetic Foot Guidance on the Diagnosis, Prognosis and Management of Peripheral Artery Disease in Patients with Foot Ulcers in Diabetes has provided the following recommendations⁶⁶:

1. Examine patients with T2DM annually for the presence of PAD including at least a detailed history and palpation of foot pulses.
2. Evaluate patients with T2DM annually for the presence of PAD by Doppler waveforms and ABPI. A value of ABPI <0.9 is considered abnormal.
3. Consider urgent vascular imaging and limb revascularisation in diabetic patients with foot ulcers showing toe pressure <30 mmHg or transcutaneous oxygen pressure <25 mmHg.
4. Consider vascular imaging and revascularisation in all diabetic patients with a foot ulcer and PAD, regardless of the findings of clinical and non-invasive tests, when the

Table 1: Classifications for the clinical staging of peripheral arterial disease.⁶²

| Fontaine classification | | Rutherford classification | | |
|-------------------------|---------------------------|---------------------------|----------|-----------------------|
| Stage | Symptoms | Grade | Category | Symptoms |
| I | Asymptomatic | 0 | 0 | Asymptomatic |
| II | Intermittent claudication | I | 1 | Mild claudication |
| | | I | 2 | Moderate claudication |
| III | Ischaemic resting pain | I | 3 | Severe claudication |
| | | II | 4 | Ischaemic rest pain |
| IV | Ulceration or gangrene | III | 5 | Minor tissue loss |
| | | III | 6 | Major tissue loss |

Source: European Stroke Association.⁵⁹

Table 2: Clinical interpretation of ABPI to assess the severity of lower limb ischaemia affected by diabetes mellitus.

| Ankle brachial pressure index | Interpretation |
|-------------------------------|---|
| >1.4 | Equivocal due to non-compressible/calcified arteries |
| 1.0–1.4 | Normal; PAD disease can be excluded in a large number of patients |
| 0.9 | Borderline; discussion with a specialist is advisable; |
| <0.9 | Abnormal: Diagnostic of PAD |
| <0.4 | Critical limb ischaemia |

ulcer does not improve within 6 weeks of non-surgical therapy.

5. Consider urgent vascular imaging and revascularisation in patients with a non-healing ulcer with either an ankle pressure <50 mm Hg or ABPI <0.5.
6. “Limb revascularisation should be aimed to restore direct flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the wound, with the aim of achieving a minimum skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg”.
7. The literature is deeply divided regarding a standard surgical approach that can be offered for revascularisation. A multidisciplinary strategy coupled with the level of surgical expertise, morphological distribution of PAD, autogenous vein or prosthesis, and patient co-morbidities play key roles in decision-making.
8. Avoid considering revascularisation in patients in which the risk-to-benefit ratio for the probability of success is not optimal.
9. All patients with T2DM and PAD should be provided with an aggressive cardiovascular risk management therapy that includes advice for the cessation of smoking, therapies for DM and hypertension, and a prescription for a statin and low-dose aspirin or clopidogrel.

The guidelines provided by the American Heart Association and American College of Cardiology Foundation recommend the control of risk factors such as DM, smoking, hypertension and hyperlipidaemia, in addition to the use of antiplatelet drugs, angiotensin converting enzyme inhibitors and statins.⁶⁷ Lifestyle changes geared towards more physical activity and a fat-free diet play major roles in preventing PAD. The Scandinavian Simvastatin Survival Study has observed that Simvastatin reduces the incidence of new claudication in patients with myocardial infarction or angina and leads to a longer pain-free walking time.⁶⁸ Currently, aspirin is recommended as a first-line antiplatelet drug. However, in the case of repeated events of ischaemia, despite antiplatelet therapy, replacing aspirin with clopidogrel or an anticoagulant or adding another antiplatelet drug may be considered.⁶⁹ A combination of the suggested therapies has been reported to be successful in delivering the optimal risk factor management in patients with symptomatic PAD.⁷⁰ Such conservative non-surgical strategies may reduce, if not eliminate, atherothrombotic events and will improve the quality of life with a better outcome.

Conclusion

There is a dramatic rise in the prevalence of DM and accompanying complications worldwide. This diabetes epidemic is a threat and burden to health-care systems and has created significant public health challenges in the Arab world including KSA. There is a proportionate rise in the prevalence of diabetes-induced PAD, an age-dependent disorder that is difficult to treat, which is caused by factors similar to that of coronary artery and cerebrovascular disease. PAD is associated with significant morbidity and a marked reduction in the quality of life. The early identification of individuals with risk factors can help to prevent the onset of PAD in patients with DM. Lifestyle changes, cessation of smoking, control of DM and hyperlipidaemia as well as the use of aspirin or clopidogrel and a statin should be instituted in an attempt to arrest the progression of PAD. In patients with PAD with critical ischaemia, endovascular revascularisation or bypass surgery should be considered. A national level concerted multidisciplinary approach, together with guideline-directed therapies, can minimize the complications of PAD. These actions would help the diabetic population improve their quality of life and minimise their risk of both loss of limb and loss of life.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

SYG conceived the concept of this research, conducted the literature review and wrote the initial draft. NJL revised and reviewed the initial write-up. Both authors approved the final manuscript.

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