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Risks for peripheral artery disease and cardiovascular disease indicated by high Ankle-Brachial index in T2DM patients

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Abstract

Objectives: The study aims to explore clinical features linked to prominent ankle- brachial index (ABI) in type 2 diabetes mellitus (T2DM), evaluating its diagnostic utility for peripheral arterial and cardiovascular diseases, and establishing cutoffs for risk prediction in the T2DM population.

Methods: The study recruited 260 outpatients with T2DM, using random sampling at Fakir Mohan Medical College, Balasore, Odisha for over 2 years from 10th April 2021 to 10th April 2023. Ankle- brachial index (ABI) measurements were taken, and participants underwent carotid arterial ultrasonography and lower limb arterial ultrasonographic examinations to assess peripheral arterial disease (PAD) and cardiovascular disease (CVD). Logit regression and ROC analysis were employed to identify independent risk factors, evaluate ABI's diagnostic potential, and determine cutoffs for predicting CVD and PAD.

Results: The study revealed a parabolic prevalence curve, demonstrating that individuals

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having either low ABI (≤ 0.9) or high ABI (> 1.3) had increased risks of cardiovascular disease (CVD). A major predisposing factor for both CVD and peripheral arterial disease in patients was the presence of ABI > 1.3, which was prevalent in 14% of the cohort. The study established ABI cutoffs of 1.43 for predicting CVD and 1.45 for PAD, exhibiting specificity rates exceeding 80%, while sensitivity varied at 37.3%.

Conclusion: The study underscores the clinical significance of a U-shaped prevalence curve for ankle–brachial index, revealing that high as well as low indices are independently associated with enhanced risks of peripheral arterial disease and cardiovascular disease in individuals with type 2 diabetes mellitus.

Keywords: Ankle-brachial index, Type 2 diabetes mellitus, Cardiovascular disease, Peripheral arterial disease

Introduction

The ankle-brachial index (ABI) serves as a reliable gauge, expressing the ratio between the cardiac blood pressure during systole detected in the lower limbs (specifically the lower leg artery or pedal artery) and the blood pressure (BP) observed in the arms [1]. This uncomplicated and non-invasive measurement proves to be a precise means for screening peripheral diseases of the artery affecting the lower extremities, standing out as the most accurate non-invasive prognostic approach for evaluating peripheral arterial disease (PAD) [2]. Compelling evidence supports the association between PAD and an elevated occurrence of coronary artery disease, a relationship that remains irrespective of the existence of other CVD predisposing factors [3].

A diminished ABI at 0.9 serves as a predictive marker for cardiac diseases, as established by extensive research [4, 5]. However, it is noteworthy that an abnormally high level of ABI also correlates with an escalated risk of CVD [6-11]. This association was observed in a comprehensive research work involving 16,493 patients who underwent testing of the arteries in the lower extremity via a non-invasive method [11]. Among them, 17% exhibited poorly compressible arteries of the lower limbs, denoted by high values of ABI, exceeding 1.4, and/or by the presence of cardiac BP during systole surpassing 255 mm of Hg [11]. Notably, individuals having larger ABI values exhibited poorer survival rates, surpassing even the

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patients having either a normal or a low level of ABI [11]. The prevalence of ABI exceeding 1.4 is more extensive and therefore carries significant prognostic implications [9-11].

Patients with T2DM face an elevated susceptibility to macrovascular ailments, with a particular emphasis on coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD) [12]. Within this diabetic population, a heightened ankle–brachial index (ABI) assumes substantial clinical significance, potentially serving as a crucial diagnostic tool for cardiovascular disease (CVD) and PAD [12]. However, there remains a scarcity of research focusing on the prevalence of cardiac and peripheral arterial diseases in patients affected with diabetes exhibiting a pronounced value of ABI, particularly in individuals with T2DM. Consequently, the current study aimed to discern the clinical characteristics linked with a high ABI and explore its prognostic utility concerning PAD and CVD among the T2DM patients.

Methods

In this cross-sectional study, 273 outpatients diagnosed with T2DM were systematically enrolled through random sampling at the Fakir Mohan Medical College, Balasore, Odisha between 10th April 2021 and 10th April 2023. Excluding specific cases, a total of 260 T2DM patients participated, with a mean age of 62.5 years and a diabetes duration of 7.4 years on an average. The gender distribution included 140 males and 120 females, all without transient complications of impaired liver function, diabetes, thyroid, recent surgical treatment, or tumors. Diagnosis of T2DM adhered to the American Diabetes Association standards and the World Health Organization criteria [13].

A survey instrument collected data on sex, patient age, weight, height, duration of diabetes, and history of smoking. The patient's corpulence index was then computed, and the questionnaire explored predisposing factors and co-existing illness such as hypertension (HTN), medication history, cerebral infarction (CI), coronary artery disease (CAD), diabetic retinopathy (DR), diabetic nephropathy (DN), and arrhythmia. To assess lower limb symptoms, the questionnaire covered sensations like soreness, burning, cramping, lameness, cold, and fatigue, complemented by a physical examination for validation.

Inclusion criteria

The inclusion criteria for this study comprised outpatients diagnosed with type 2 diabetes mellitus (T2DM) recruited through random sampling from Fakir Mohan Medical College, Balasore, Odisha between April 2021 and April 2023. Patients included were those without acute complications of liver dysfunction, diabetes, tumors, recent major surgery, or thyroid disease.

Exclusion criteria

Individuals with type 1 diabetes, abnormal glucose regulation, normal glucose tolerance, previous arterial revascularization of lower limbs, or spinal stenosis/ protrusion of the lumbar intervertebral disc were excluded. Additionally, those with short-term complications of diabetes, cancer, liver dysfunction, recent major surgery, or thyroid disease, were also excluded from participation.

Diagnostic Imaging Assessments

During the physical examination, lower limb clinical manifestations, including bruising, swelling, dryness, ulcers, blistering, arterial pulse, and presence of gangrene, were documented. Dorsal pedal and posterior leg pulses were rated as 0 for normal and 1 for diminished or absent, based on palpation. Patients with impaired ankle–brachial index underwent Doppler ultrasonography, with 39 undergoing arterial ultrasound of lower legs and 15 having magnetic resonance angiography (MRA).

Comprehensive Laboratory Profiling

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Blood drawn from the veins obtained post nocturnal fasting and after postprandial were subjected to a comprehensive laboratory evaluation. This included measurements of blood glucose after fasting and plasma glucose levels postmeal, insulin concentration during fasting, glycated hemoglobin (HbA1c), liver function markers (AST, ALP, ALT), glycated serum albumin (GA), renal function indicators (BUN, UACR, GFR), hemoglobin levels, and lipid profile. Homeostasis model assessment (HOMA) for beta-cell (HOMA-B) function and for insulin resistance (HOMA-IR) was estimated.

The blood glucose level was determined using the glucose oxidase assay, insulin levels were assessed through radioimmunoassay, and the measurement of HbA1c was conducted using high-pressure liquid chromatography. Kidney and liver function, as well as GA, were measured using automated analyzers. Urinary creatinine and albumin were assessed via immunoturbidimetry and enzymatic methods, respectively. Glomerular filtration rate (GFR) was quantified by scanning with the help of radioactive isotope of Technetium-99, and total GFR was calculated by summing left and right kidney values.

Ankle-Brachial Index Assessment

Utilizing the two-way Doppler blood – flow detector, the measurement of ABI was conducted. Trained investigators carried out ABI assessments under standardized conditions, ensuring consistency and accuracy. The examination took place after a minimum 5-minute relaxation period while lying down in the supine position, ensuring the upper body is as horizontally aligned as achievable.

ABI was computed for each leg and subsequent analysis was carried out using the least value of ABI. The levels of ABI were then categorized into three classes: ABI lesser than or equal to 0.9; 0.9 lesser than ABI lesser than or equal to 1.3, and ABI greater than 1.3, facilitating a comprehensive classification for further interpretation and study analysis.

Vibration Perception Threshold Assessment:

To measure vibration perception threshold, a neurothesiometer was employed consistently by the same technician. Patients assumed a supine position in a tranquil environment with closed eyes. The vibration sensor was positioned on a skeletal region on the back side of the tip bone of the initial toe. The voltage was gradually increased by 5-volt increments, and the Vibration Perception Threshold (VPT) was noted down to mark the moment the patient first sensed vibration. After repeating this test thrice, the average value was calculated to get the final VPT. Subsequent analysis was carried out using the larger VPT value of either one of the limbs. Based on the VPT values, it was further categorized as abnormal (> 25 volt), intermediate (16 to 25 volt), and normal (< 15 volt).

Peripheral Arterial Disease (PAD) and cardiovascular disease (CVD) Diagnosis

The recognition of pre-existing cardiac conditions relied on recorded accounts of neurovascular disease and CAD. New asymptomatic CVDs were characterized by the plaque formation in the lower limb arteries or carotid extremity, as determined in accordance with our previous study [14]. Patients without a prior history of peripheral arterial disease were categorized as having newly diagnosed PAD if ultrasonography or magnetic resonance angiography results indicated occlusion or stenosis in the lower limb arteries.

Statiscal analysis

Data analysis was conducted using IBM SPSS 20.0, with quantitative variables reported as mean ± standard deviation and discrete variables presented as percentages. Comparative analyses utilized ANOVA, Mann-Whitney tests, with Fisher exact tests for qualitative variables, or t-tests. Logit regression was used to assess the predisposing factors for CVD and PAD. Significance of the test was established with a P lesser than 0.05.

Results/Outcomes of the study

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Varied ABI Categories and Clinical Indications in Lower Limbs

In comparison to normal group (ABI = 0.9 to 1.3), the < 0.9 and > 1.3 groups exhibited higher proportions of clinical symptoms in lower limbs, including pain, coldness, cramping, weakness, puffiness, and lameness (P < 0.05). Notably, the 0.9 group showed the largest populace, with the >1.3 cohort following closely. In a similar manner, the former also displayed the largest populace of various clinical manifestations such as contusion, blistering, inflammation, gangrenous malformation, arterial pulse and ulceration (P < 0.05), excluding infections by fungi. In contrast, the > 1.3 cohort ranked behind this in these clinical signs.

Diverse Clinical Features Across Distinct ABI Categories

Within the > 1.3 cohort, several factors, including age, diabetes duration, HbA1c, and vibration perception threshold, exhibited higher values compared to the 0.91 to 1.3 group (P < 0.05). These parameters were, however, insignificant when compared to those observed in the 0.9 group (P < 0.05). The > 1.3 group displayed the highest Body Mass Index (BMI) among the groups and also demonstrated a higher Glomerular Filtration Rate (GFR). Notably, liver function markers and renal function indicators representing non-normally distributed quantitative attributes, showed prominent variations among the cohorts (P < 0.05). Moreover, the 0.91 to 1.3 group consistently exhibited the lowest values in these parameters, with the exception of LDL-C.

Incidence of Vascular Complications Across Varied ABI Categories

Prevalence of vascular complications, assessed by various diagnostic modalities, differed significantly among the three ABI classes (P < .05). In the 0.9 cohort, carotid arterial occlusion/ stenosis, CI, and CAD, had the largest prevalence when compared to the > 1.3 cohort. Analysis across genders, age categories, and HbA1c levels revealed significant differences in PAD and CVD pervasiveness among the ABI groups (P < 0.05). The < 0.9 group consistently showed

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the highest incidence rates, except for peripheral arterial disease in the patients younger than 50 years and CVD in patients belonging to 50 – 60 years (P > 0.05) (Table 1).

Table 1: Cardiovascular and Peripheral Arterial Disease Rates in Relation to Three Ankle–Brachial Index (ABI) Categories

	ABI			
Group	≤ 0.91	0.91 - 1.3	> 1.3	*P-value*
Men	16	110	14	
CVD (%)	9 (59.0)	17 (16.1)	4 (34.0)	<.001
PAD (%)	9 (58.2)	3 (2.7)	2 (15.5)	<.001
Female	16	94	10	
CVD (%)	8 (55.0)	20 (22.7)	3 (36.1)	<.001
PAD (%)	6 (40.3)	1 (1.6)	1 (8.3)	<.001
Age lesser than 50 (yrs)	2	36	18	
CVD (percentage)	1 (48.1)	1 (1.7)	1 (4.5)	< 0.001
PAD (percentage)	0 (0)	1 (1.0)	1 (3.9)	0.270
50 ≤ age < 60, years	21	65	46	
CVD (percentage)	5 (21.7)	8 (11.1)	2 (18.4)	0.280
PAD (percentage)	10 (46.6)	1 (1.5)	2 (11.9)	< 0.001
60 ≤ age < 70, years	51	66	74	
CVD (percentage)	25 (48.0)	14 (22.4)	6 (47.6)	< 0.001
PAD (percentage)	26 (52.0)	1 (1.7)	2 (16.6)	< 0.001
Age ≥ 70, years	23	36	37	
CVD (percentage)	14 (63.0)	15 (42.2)	6 (44.9)	< 0.001
PAD (percentage)	11 (49.7)	1 (5.1)	4 (11.8)	< 0.001
HbA1c < 6.5 %	24	46	41	
CVD (percentage)	13 (53.2)	7 (16.1)	8 (18.5)	< 0.001
PAD (percentage)	10 (40.7)	1 (1.9)	3 (6.3)	< 0.001
6.5 % < HbA1c < 7.5 %	54	51	47	
CVD (percentage)	33 (62.0)	10 (21.7)	17 (35.5)	< 0.001
PAD (percentage)	26 (50.9)	1 (1.5)	9 (18.1)	< 0.001
HbA1c > 7.5 %	13	72	57	

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CVD (percentage)	8 (61.3)	13 (19.2)	16 (27.1)	< 0.001
PAD (percentage)	6 (50.5)	1 (2.1)	4 (7.1)	< 0.001

Determinants of both the cardiac diseases (PAD and CVD)

Through logit regression analysis, examination of independent variables, including sex, age, corpulence index, TG, HbA1c, TC, LDL-C, HDL-C, and timeframe of diabetes, highlighted distinct contributors to the risk of both the cardiac diseases in the cohort having high ABI. Notably, independent risk factors for CVD development encompassed a high ABI (> 1.3; Wald: 7.195), elder age (Wald: 10.385), timeframe of diabetes (Wald: 5.894), and hypertension (Wald: 8.596) ($P < .05$). Similarly, for PAD, independent risk factors included a high ABI (> 1.3; Wald: 5.412) and timeframe of diabetes (Wald: 4.351) ($P < 0.05$).

Associations Between High ABI and CVD/PAD

ROC analysis revealed a cutoff of 1.43 for high ABI in predicting CVD, yielding a Youden index of 0.17, with 37.3% sensitivity and 80.1% specificity. Beyond this threshold, the adjusted risk of CVD significantly increased to 2.25 (1.43 to 3.54, $P < .001$). For PAD prediction, the cutoff for high ABI (>1.3) was 1.45, with a Youden index of 0.50, 64.7% sensitivity, and 84.9% specificity. At this level, the adjusted risk of PAD markedly rose to 6.97 (4.06 to 11.98, $P < .001$). Exceeding 1.43 and 1.45, the odds ratios (OR) for CVD and PAD, adjusted for various factors, were 2.25 and 6.97, respectively ($P < .001$).

Discussion

The ankle–brachial index (ABI) serves as a pivotal technique in peripheral arterial disease (PAD) screening and monitoring. The broader implications of this tool extend to the evaluation of diseases and diagnoses of stroke and coronary artery disease [16]. The study's findings align with previous evidence, indicating that patients with either low ABI (lesser than 0.9) or high

ABI (exceeding 1.3) face heightened mortality risks. Notably, high ABI is often associated with medial artery calcification, positively correlating with CAD risk [15]. European studies have underscored the predictability of ABI >1.4 in forecasting increased cardiovascular events [16].

The current investigation focuses on unravelling the clinical characteristics of high ABI, specifically examining its prognostic utility in cardiovascular disease and PAD, juxtaposed with normal ABI and low ABI scenarios. A comprehensive comparison across the three ABI groups unveils significant differences in both symptomatic presentation and in lower limb manifestations. The prevalence pattern reveals low ABI as predominant, succeeded by high ABI, forming a parabolic curve. Strikingly, individuals with high ABI exhibit lower limb ischemic symptoms akin to those with ABI less than 0.91, including cold sensations, neuralgia, lameness, ulcer, inflammation, contusion, puffiness, and weakened or disappeared arterial pulse. Neuropathic indicators like cramping, anesthesia, deformity, and drying are also evident in both low and high ABI cases.

Further examination of the symptoms in the 3 cohorts of ABI reveals distinct profiles. Individuals with low ABI tend to be older, have a longer duration of type 2 diabetes mellitus (T2DM), reduced BMI, poorer blood glucose regulation, compromised nutritional, reduced kidney function, and more severe nerve damage, as identified by vibration perception threshold (VPT), in contrast to the normal cohort. Conversely, those in the high ABI cohort present with a higher BMI, better blood glucose regulation, and improved nutritional status, consistent with previous research [7, 11, 17].

Recent studies have highlighted the incidence of extremely low or high ABI in individuals with both T2DM and CVD. Building on previous work, our study introduces carotid artery ultrasonography and lower limb arterial ultrasonographic assessment to enhance the identification of atherosclerosis in diabetic individuals [14]. The pervasiveness of blood vessel-related issues is further explored in various ABI cohorts, revealing a U-shaped curve in which

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patients with high ABI exhibit a higher occurrence rate of CVD comparable to that of the normal group but lesser than that of the group with ABI lesser than 0.91 [18-20].

Notably, smoking, a known predisposing factor for PAD and CVD, did not exhibit prominent variations in the three ABI cohorts in this study. Logit regression analysis identified high ABI (> 1.3) as a separate predisposing factor for both the cardiac diseases. ROC analysis pinpointed an ABI > 1.43 as predictive of cardiovascular ailments, with a 2.71-fold increased risk, boasting enhanced specificity (80.1 %) but diminished sensitivity (37.3 %). Similarly, an ABI >1.45 was identified as predictive of PAD, with a 7.54-fold increased risk compared to normal ABI, demonstrating high specificity.

The adjusted risk analysis further substantiates the connection between high ABI and elevated risks, revealing a 1.25-fold greater risk of cardiovascular ailments in the > 1.43 ABI cohort and a 5.97-fold greater chance of getting PAD in the > 1.45 ABI group compared to normal ABI. Thus, an ABI >1.43 and 1.45 emerges as reliable indicators for forecasting PAD and CVD risks in the T2DM patients.

Despite the insightful contributions offered by this investigation, it is essential to recognize various constraints inherent in the study. The cross-sectional nature and reliance on some retrospective data introduce potential biases. Longitudinal prospective studies are essential for a more comprehensive understanding of ABI dynamics in diabetes patients. Additionally, the impact of aging on vascular calcification cannot be entirely excluded, particularly in the older subjects included in the study.

Conclusion

The study focussing on the use of High Ankle-Brachial index as an indicator of cardiovascular and Peripheral Arterial Disease in patients with Type-2 Diabetes mellitus highlights distinctive symptoms associated with high and low ankle–brachial index (ABI) in type 2 diabetic

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individuals. The U-shaped prevalence curve underscores the heightened risk of cardiovascular disease (CVD) in individuals with either low or high ABI, with high ABI serving as an independent predisposing factor for both CVD and peripheral arterial disease (PAD). The identified ABI cutoffs of 1.43 and 1.45 present reliable thresholds for predicting CVD and PAD risks in the T2DM population. Despite its limitations, this research underscores the valuable diagnostic utility of ABI in assessing vascular complications and informs risk assessment strategies in this patient demographic.

Limitations

The limitation of the current study includes its cross-sectional design, which precludes establishing causality, and the reliance on retrospective data for certain indicators, introducing the possibility of missing information. Additionally, the influence of aging on calcification of blood vessels, especially in older subjects, may affect ankle–brachial index (ABI) measurements and contribute to potential confounding factors.

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