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Original research

A high ankle-brachial index is associated with obesity and low serum 25-hydroxyvitamin D in patients with diabetes

Barbara Depczynski[a,b,*], Tamara Young[a], Christopher White[a,b]

[a] Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, New South Wales 2031, Australia
[b] University of New South Wales, Faculty of Medicine, University of New South Wales Sydney, New South Wales 2052, Australia

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ABSTRACT

Peripheral artery disease (PAD), when present with diabetes, is associated with significant morbidity and mortality. The spectrum of PAD in diabetes includes atherosclerosis with stenotic disease; and diffuse medial calcification with non-compliant arteries, as reflected by high ankle brachial index. The clinical characteristics of a high ABI are less well characterized than that of low ABI.

The aim of this study was to determine the unique clinical phenotype of patients with diabetes who have high ankle brachial index (ABI) reading. We performed a cross sectional observational study including 360 patients. Subjects were grouped according to normal ($\geq 0.8 \leq 1.3$), low (< 0.8) or high ABI (> 1.3) result. Subjects with high ABI were characterised by higher BMI, higher waist/height ratio (WHtR), and lower serum lower vitamin D. Although reduced renal function and neuropathy was present more frequently in those with high ABI, this was also the case in those with low ABI. Similarly to those with low ABI result, a high ABI result was associated with increased risk of diabetic foot complications including amputation. When adjusted for known risk factors for PAD, higher WHtR and lower vitamin D were significant predictors of high ABI. These results suggest an association between increased WHtR and low vitamin D with high ABI; whether there is a causal relationship requires further exploration.

Introduction

Peripheral arterial disease (PAD) is a significant cause of morbidity in patients with diabetes and identifies those at increased of cardiac death [1].

Measurement of ankle-brachial index (ABI) is a non-invasive investigation for the presence of PAD [2,3]. In those with diabetes, screening in patients 50 years or older or in younger patients with risk factors for PAD is recommended [2]. The spectrum of PAD includes atherosclerosis with stenotic disease, and arteriosclerosis with non-compliant arteries due to diffuse medial calcification [3].

A low ABI is associated with increased total mortality, cardiovascular disease mortality and cardiovascular morbidity including myocardial infarction and stroke [4].

A high ABI result suggests the presence of non-compliant, calcified arteries [3]. A high ABI is associated with an increased risk of stroke and congestive heart failure as well as poorer quality of life [5].

Traditional vascular risk factors can delineate those at risk for stenotic disease [4]. Chronic kidney disease and diabetes are risk factors for presence of high ABI [6] but whether there are additional characteristics of those with diabetes who have a high ABI, as compared to those with normal or low ABI requires elucidation. The aim of this study was to describe the clinical associations of high ABI in a cohort with diabetes.

Methods

This was a retrospective chart review. The study population consisted of adult patients attending diabetes outpatient department at a tertiary referral hospital in Australia. Patients were eligible if an ABI measurement had been performed in 2 years preceding the chart review. Clinical and laboratory variables performed at the time of the ABI reading were used for this analysis. Patients were ~~assignedtogroup~~ considered to have a normal ABI if ABI was $\geq 0.8 \leq 1.3$; a low ABI if the result was < 0.8 and considered to have a high ABI if it was above 1.3 [4]. ABI was measured after 5 min of supine rest, by using manual blood pressure cuff and hand held Doppler (Huntleigh Dopplex D900). Where ABI readings were discordant between left ankle:left brachial versus right ankle:right brachial results, patient was considered to be in the low ABI group [3].

* Corresponding author at: Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, New South Wales 2031, Australia.
E-mail address: Barbara.depczynski@health.nsw.gov.au (B. Depczynski).

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Hypertension was defined as either systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher, or current use of an antihypertensive agent. Presence of coronary artery disease (CAD), history of stroke or foot complications was based on documentation by treating physician. Assessment of peripheral neuropathy was based on biothesiometer reading when applied to the first metatarsal phalangeal joint. A reading above 25 V is regarded as abnormal, and predictive of subsequent foot ulceration [7]. Where the maximum vibration was not able to be detected (50 V), a value of 70 V was entered, to allow analysis of biothesiometer readings as a continuous variable. Height and weight was measured with patients in light clothing and no shoes. Waist was measured midway between the lowest ribs and the iliac crest. The CKD-EPI formula was used to determine the estimated glomerular filtration rate (eGFR).

Data was expressed as percent or mean ± standard deviation. Statistics were performed using SPSS Version 24. Kruskal-Wallis *H* test was used for comparisons between groups for continuous variables. Where there were significant differences, post hoc analysis was performed using Dunn's procedure with a Bonferroni adjustment. For categorical variables, x^2 test was performed and if there was a significant difference across groups, comparisons were then made with normal ABI cohort. After visual inspection of scatterplots of the ABI result as compared to variables of interest, if a linear relationship was seen, correlation was determined by Pearson's coefficients. A p value < 0.05 was deemed statistically significant. Given that this was a retrospective study and all results are exploratory, corrections for multiple comparisons were not made. Stepwise logistic regression was performed to explore the contribution of any predictive variables on presence of high ABI.

Ethics approval was obtained from South Eastern Sydney Local Health District Human Research Ethics Committee. For this retrospective study, the need for informed consent was waived by the ethics committee.

Results

360 patients had results of ABI study available; ABI was normal in 249, low in 46 and high in 65 patients. 93.6% of the whole cohort had type 2 diabetes mellitus (T2DM) and the remainder had type 1 diabetes. Data for patients in each ABI category are given in Table 1. Those in low or high ABI groups were older than those with normal ABI. Those with low or high ABI had significantly longer duration of diabetes as compared to those with normal ABI.

The high ABI group had a higher body mass index (BMI) as compared to those with normal or high ABI (31.7 ± 5.4 versus 29.5 ± 5.2 kg/m2 in normal, $p < 0.01$) and higher waist-height ratio (WHtR) (66.7 ± 7.7 versus 61.9 ± 8.2 cm/m, $p < 0.01$).

HbA1c, total cholesterol, HDL or triglycerides did not differ across the 3 groups. Presence of hypertension was higher in those with abnormal ABI. Of the low ABI group, 20.5% were current smokers as compared to 12% of normal ABI cohort and 3.4% of high ABI cohort. Statin or anti-hypertensive use was highest in those with any abnormal ABI. Both those with low or high ABI had lower eGFR (67.2 ± 18.8, 60.1 ± 28.5 versus 76.4 ± 24.3 mL/min/1.73 m2; $p < 0.05$ for low or high versus normal) but the decline in eGFR over the preceding 5 years was greatest in those with high ABI (0.19 ± 0.26 mL/min/1.73 m^2) versus normal ABI group (0.05 ± 0.23 mL/min/1.73 m^2) or low ABI group (0.09 ± 0.20 mL/min/1.73 m^2). Calcium-phosphate (Ca.PO4) product was higher in low ABI group as compared to normal ABI group (2.87 ± 0.56 versus 2.63 ± 0.53 mmol/L.mmol/L) but Ca.PO4 product was not increased in the high ABI group (2.70 ± 0.44 mmol/L.mmol/L). Total serum alkaline phosphatase (SAP) was significantly different across the 3 groups (74.2 ± 18.3 for normal, 79.9 ± 22.3 for high ABI group, and 82.6 ± 24.9 U/L for low ABI group, $p < 0.01$ across groups). Serum 25 hydroxyvitamin D (vitamin D) was lower in high ABI group as compared to normal (49.2 ± 20.4 versus 61.1 ± 22.6 nmol/L, $p < 0.01$). Biothesiometer readings were similarly higher in low and high ABI groups (47 ± 16 V for low, 50 ± 18 V for high versus 30 ± 16 V in normal, $p < 0.01$). Foot complications were more frequent in high and low ABI groups.

Visual inspection of scatterplot of ABI revealed a linear relationship between duration of diabetes, WHtR, vitamin D and inverse U relationship with eGFR. There was a modest positive correlation between ABI and WHtR ($r = 0.257$, $p < 0.01$); and a negative correlation with vitamin D ($r = -0.145$, $p < 0.05$). Relationship with duration of diabetes did not reach significance ($r = 0.094$, p 0.06). No linear relationship was seen with patient's age, HbA1c, lipids, calcium.phosphate product, SAP, blood pressure reading or biothesiometer reading.

Binary logistic regression was performed using a stepwise analysis to examine the likelihood that a patient had a high ABI as compared to

Table 1
Clinical and laboratory characteristics of patients according to ABI category.

Characteristics	Normal ABI ≥ 0.8 ≤ 1.3	Low < 0.8	High > 1.3
Patient number	249	46	65
Age Years	63.3 ± 11.9	70.7 ± 8.7*	70.5 ± 8.9*
Male percent	49.4	69.6	72.3
Duration of diabetes years	11.7 ± 9.3	18.2 ± 12.1*	18.4 ± 9.6*
BMI kg/m2	29.5 ± 5.2	29.3 ± 5.0	31.7 ± 5.4*#
Waist/height cm/m	61.9 ± 8.2	61.9 ± 6.9	66.7 ± 7.7*#
n	215	30	51
Hba1c percent	7.7 ± 1.5	7.7 ± 1.3	8.1 ± 1.8
Hba1c mmol/mol	61 ± 4.5	61 ± 8.3	65 ± 8.0
Total cholesterol mmol/L	4.3 ± 1.2	4.0 ± 1.2	4.0 ± 1.2
n	237	45	59
HDL mmol/L	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.3
n	233	36	57
Triglycerides mmol/L	1.8 ± 1.2	1.9 ± 1.4	1.9 ± 1.1
n	233	45	59
eGFR mL/min/1.73 m2	76.4 ± 24.3	67.2 ± 18.8^	60.4 ± 28.5^
eGFR 5 years prior mL/min/1.73 m2	80.1 ± 23.2	74.0 ± 19.6	70.5 ± 26.3^
Urine albumin/creatinine ratio mg/mmol	19.0 ± 83.4	25.5 ± 81.3^	23.2 ± 51.6
n	210	34	57
Calcium.phosphate product mmol/L.mmol/L	2.63 ± 0.53	2.87 ± 0.56^	2.70 ± 0.44
n	211	36	59
Serum alkaline phosphatase mmol/L	74.2 ± 18.3	82.6 ± 24.9	79.9 ± 22.4##
n	238	44	63
25 hydroxy-vitamin D	61.1 ± 22.6	59.2 ± 18.3	49.2 ± 20.4*
n	184	32	51
Insulin use percent	48.2	69.6	60
Statin use percent	74.3	89.1^	90.8^
Hypertension percent	75.5	97.8^	90.8^
Smoking%			
Never	58.4	27.3	50
Current	12.2	20.5	3.4##
Prior	29.4	52.3	26.6
Coronary artery diseasepercent	17.3	47.8^	30.8^
Stroke percent	5.6	17.4^	13.8^
Foot Ulcer percent	4.1	32.6^	16.9^
Osteomyelitis percent	3.6	21.7^	12.3^
Lower limb Amputation percent	0.8	10.9^	7.7^
Biothesiometer reading volts	30 ± 16	47 ± 16*	49 ± 17*
n	227	43	61
Diabetic retinopathy percent	21	34.8^	41.9^

n = number available for analysis if less than complete set.
* $p < 0.01$, as compared to normal ABI group.
# $p < 0.05$, as compared to low ABI group.
^ $p < 0.05$ as compared to normal ABI group.
$p < 0.05$ across groups.

Table 2
Logistic regression predicting likelihood of high ABI reading.

Variable*	B coefficient	SE	Wald	P	Odds ratio	95% confidence interval
WHtR*	0.072	0.03	5.626	0.018	1.074	1.013–1.14
Vitamin D#	−0.037	0.013	7.813	0.005	0.964	0.939–0.989

* adjusted for age, sex, duration of diabetes, eGFR, smoking status, biothesiometer reading, use of statin, presence of hypertension.

adjusted for age, sex, duration of diabetes, eGFR, smoking status, biothesiometer reading, use of statin, presence of hypertension, and WHtR.

normal ABI group. The normal ABI group was used as the reference. A model was developed to explore the role of variables in predicting the presence of high ABI. The model included adjustment for sex, duration of diabetes, age, eGFR, smoking status (current or prior smoking versus no smoking), biothesiometer reading, use of statin and presence of hypertension as all these variables differed between the 2 groups and there is evidence for their role in development of increased ABI [4,5]. WHtR and vitamin D were added in a stepwise fashion. With adjustment, both higher WHtR and lower vitamin D remained significant predictors, as shown in Table 2.

Discussion

In this cross sectional cohort study of patients with diabetes, we have shown that those with a high ABI are characterized by higher BMI, higher WHtR, and lower vitamin D. Although eGFR was lower and vibration threshold higher in those with high ABI, this was no different to the low ABI group. Both high and low ABI groups had greater history of foot complications.

Those with low ABI were older than those with normal ABI, with longer duration of diabetes. Differing to prior reports [4], the only differences in traditional vascular risk factors seen were for hypertension and smoking history; the lack of difference with lipids may reflect treatment effects as statin use did differ being more frequent in those with low and high ABI. Coronary artery disease and history of stroke were more frequent in those with high ABI.

Those with diabetes and a high ABI were characterised by visceral adiposity as suggested by higher WHtR. That obesity has not been shown to be a risk factor for stenotic PAD [4], is supported by our finding were there was no difference in BMI between those with low and normal ABI; only those with high ABI had higher BMI and higher WHtR. Vascular inflammation is a potential mechanism via which visceral adiposity promotes arterial stiffness [4].

Vitamin D was lower in high ABI group. Low vitamin D has been described in association with cardiovascular disease [8] and is particularly associated with increased arterial stiffness [9]. Although it has been proposed that obesity is associated with vitamin D deficiency due to sequestration of hormone into adipose tissue [10], since the relationship of 25(OH)D levels with ABI remained after adjustment for adiposity, it is likely that this relationship is independent of fat sequestration of vitamin D.

High SAP can be seen in vitamin D deficiency, and may account for increased SAP seen in high ABI cohort, however high SAP was also seen in low ABI group, who did not have reduced vitamin D. Alkaline phosphatase promotes vascular calcification [11], and a higher SAP has been shown to be an independent predictor for vascular events [12].

Chronic kidney disease (CKD) is a risk factor for PAD [4], and both high and low ABI groups were associated with a lower eGFR. Vascular stiffening present in high ABI cohort may contribute to CKD as those with high ABI had the greatest decline in eGFR over the preceding 5 years. CKD alone is not likely to account development of high ABI as reduced eGFR was present in both low and high ABI cohorts; and, despite adjusting for eGFR and other vascular risk factors, WHtR added to the predictive power of our model for presence of high ABI.

It has been proposed that high ABI reflects the end result of diabetic neuropathy resulting in sympathetic deinnervation [13]. Both high and low ABI was associated with peripheral neuropathy; an association with neuropathy and high ABI may reflect diabetes chronicity. Thus we confirm the utility of ABI measurement in delineating a group of patients with unfavourable outcomes.

Despite effective obesity therapies not always being offered as part of diabetes care [14], our results support the utility of clinical studies to determine whether weight management is useful for reducing ABI since visceral adiposity is associated with high ABI and currently there are no pharmacotherapies for reversing high ABI [6].

There are several limitations to this study. Data set is incomplete, and likely subject to unmeasured bias. Laboratory results were from more than one pathology provider, thus there is likely to be heterogeneity in assay methods for some analytes. Traditional cardiovascular risk factors of smoking and hypertension are strong risk factors for the development of PAD, with variable associations seen with dyslipidaemia [4]. The limited relationships seen in our study may reflect the impact of treatment or unmeasured biases. Another limitation is that there were more men in our cohort than women, yet there is no male predominance in our clinic attendance. In our study, a further limitation is that a high ABI although highly specific is poorly sensitive for the detection of radiologically detectable medial arterial calcification [15], and so some patients in normal category may have stenotic disease with diffuse calcification.

In summary, we demonstrate that a high ABI, suggestive of diffuse medial calcification affecting the lower limb vasculature, is associated with lower serum vitamin D and visceral adiposity, as suggested by increased WHtR. Further exploration in the population with abnormally high ABI is warranted to determine whether these associations are causal and the mechanisms via which they may affect ABI, given the current lack of therapies for diffuse medial calcification.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcte.2018.02.001.

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