Is the advancement of diabetic angiopathy evaluated as ankle-brachial index directly associated with current glycaemic control?

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Abstract

Introduction and objective: Diabetic patients are at high risk for peripheral arterial disease (PAD) characterized by symptoms of intermittent claudication or critical limb ischemia. Measurement of ankle-brachial index (ABI) has emerged as the diagnostic tool of choice, because it is relatively simple, non-invasive and inexpensive. It is also an independent marker of increased morbidity and mortality from cardiovascular diseases. The aim of the presented study was to assess the relationship between current glycemic control defined by glycated hemoglobin (HbA_{1c}) level, and quantitative changes in the arteries of the lower limbs in patients with type 2 diabetes.

Materials and methods: 175 patients with type 2 diabetes hospitalized in the Diabetology Ward were studied. VENO Doppler and a sphygmomanometer were used to assess blood flow.

Results: The average level of HbA_{1c} was assessed at 8.48%. Although the average level of ABI indicator was 1.20 (normal), only 45% of evaluated patients had their individual index within the normal range. Signs of ischemia were found in 17.7% of examined subjects. There was no conclusive correlation between ABI and HbA_{1c} levels.

Conclusions: The current level of glycemic control evaluated as HbA_{1c} has no direct impact on the advancement of diabetic angiopathy evaluated as ABI.

Key words

type 2 diabetes, diabetic angiopathy, peripheral arterial disease, ankle-brachial index, glycated haemoglobin

INTRODUCTION

One of the most feared consequences of poorly-controlled diabetes mellitus is amputation of a lower limb [1]. It occurs 12 times more often in patients with diabetes than in those without it [2]. One of the main causes of limb amputation is peripheral arterial disease (PAD) [3] which is present in 50% cases of patients with diabetic foot ulcer [1]. PAD is also a risk factor of foot infection [4]. Both PAD and infections are listed among the major contributors of leg amputations if a diabetic foot ulcer is present [5].

Diagnosis of PAD among diabetic patients has its limitation due to diminished clinical manifestations of the disease and diagnostic methods. A high level of specificity (83.3–99.0%) and accuracy (72.1–89.2%) of the method in detecting ≥50% stenosis was reported for an ankle-brachial index (ABI) ≤0.90 [6].

There is an established relationship between diabetes and ABI. In age and gender adjusted groups in the USA, the odds ratio for diabetes prevalence among people with low ABI (below 0.9) was highest (2.71) compared with hypertension (1.75) or hypercholesterolemia (1.68) [7]. Diabetes was also more common among American Indians with low and high ABI in the Strong Heart Study [8].

Some of the studies describe low ABI as a good indicator of cardiac death risk among diabetic patients [9]. On the other hand, elevated glycaemia evaluated as a high level of HbA_{1c} is recognized as one of the major risk factors of microvascular complications in type 2 diabetes [10]. The influence of elevated glycaemia on macrovascular complications is not unequivocally established, especially among patients with already existing complications and long history of prolonged hyperglycaemia [11, 12]. Therefore, it would be interesting to evaluate the relationship between hyperglycaemia and atherosclerosis, presented as the two simple clinical measurements (HbA_{1c} and ABI), especially among type 2 diabetics with long-term established diabetes.

OBJECTIVE

The aim of the study was to establish the prevalence of ABI abnormalities, and to assess the potential relationship between the level of HbA1c and ABI among hospitalized type 2 diabetic patients in the Diabetology Ward.

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MATERIAL AND METHODS

A total of 175 patients with type 2 diabetes admitted to the Diabetology Ward between 14 December 2009 and 9 February 2011 due to elevated plasma glucose concentration were examined, and whose illness could not be controlled in ambulatory care provided by primary health care physicians.

A VENO Doppler (Sonomed, Warsaw, Poland) was used to assess blood flow in the lower limbs. Systolic blood pressure was measured on the right arm (brachial artery), and both right and left ankles (posterior tibial arteries). The measurements were performed in the supine position.

Left and right ABI measurements were obtained by dividing mean systolic blood pressure in the right and left ankle by mean systolic blood pressure in the arm. The worst of the 2 values was used to define ABI for each individual. If the pulses were absent, ankle blood pressure measures were taken on the dorsal pedal artery – this situation occurred in 2 cases.

PAD was defined as an ABI <0.90 in either leg. The increased ABI was defined as >1.3. ABI was measured during the first 2 days from admission to hospital. Glycated hemoglobin (HbA$_{1c}$) was also determined on admission to hospital. The measurements were performed by accredited laboratory methods using the standardized DCCT/NGSP method, which is one of the recommended methods [13]. The test incorporates a latex-enhanced competitive turbidimetric immunoassay, which determines HbA1c concentration with a colorimetric quantification of total haemoglobin.

Statistical analysis was performed using STATISTICA 8.1 Stat-Soft package. Descriptive statistics of analyzed variables includes: average, median, standard deviation, bottom and upper quartiles, maximum, minimum and skewness. Variables distribution was tested by normality Kolmogorov-Smirnof and Lillefors statistics. Parametric analysis of variance and non-parametric Kruskal-Wallis statistics were used to test the difference of continuous variable values between discrete variable categories. Respectively, parametric Pearson correlation and non-parametric Spearman correlation were used to test 2 continuous variables coincidence. Homogeneity of variance was checked with Levene and Brown-Forsythe tests. For statistical analysis, the levels of ABI on both legs were evaluated as separate values (350 measurements).

RESULTS

73 females and 102 males were examined, mean age 61.63±10.17 years (63.16±10.58 and 60.53±9.76, respectively). The mean duration of diabetes was 14.73±10.03 years.

According to ankle-brachial index, the patients were divided into groups of stenosis/ischemia (ABI below 0.9 at least on one limb), excessive rigidity (ABI over 0.9 at least on one limb, excluding ischemia group), and normal (ABI on both limbs within 0.9-1.3) (Tab. 1).

Descriptive statistics of the analyzed variables (HbA1c and ABI) in the analyzed population are shown in Table 2. Derogation from the normal distribution was found for both HbA1c and ABI (p <0.01 in the Kolmogorov-Smirnov and Lillefors tests), caused by marked skewness (skewness statistic: 1,499 and 1,602, respectively).

The first step was a visual analysis of the relationship between both variables, depending on the scatterplot diagram (Fig. 1), but any clear relationship, both of the linear and non-linear types, was not found. The visual assessment was confirmed according to Pearson correlation test -0.062 (p≈0.2) and non-parametric Spearman rank correlation test -0.069 (p≈0.2)

Table 1. Prevalence of blood flow disturbances among the studied patients

ABI		females	males	both
low (stenosis/ischemia)	n	10	21	31
	%	13.70	20.59	17.71
normal	n	42	37	79
	%	57.53	36.27	45.14
elevated (excessive rigidity)	n	21	44	65
	%	28.77	43.14	37.14

Table 2. Descriptive statistics of analyzed variables in examined population

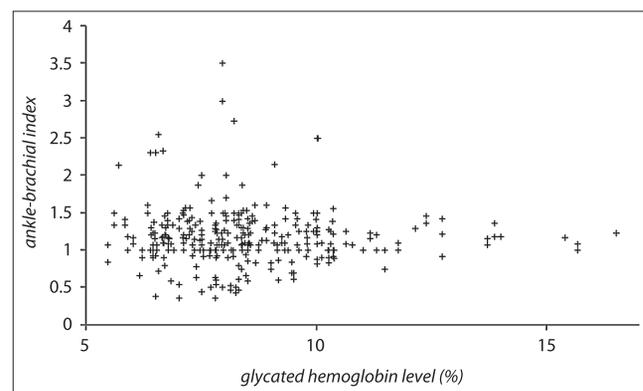|	n	median	min.	max.	average	SD
HBA1C	175	8.18	5.47	16.5	8.48	1.91
ABI	350	1.17	0.33	3.50	1.20	0.40

Figure 1. Scatter plot of ABI vs. Hba1c level (350 measurements in 175 patients)

In the second stage, glycated hemoglobin level variability was analyzed in the type 2 diabetic patients in the 3 groups divided according to ABI (Tab. 3). Due to the inequality of variance in the groups (p≈ 0.00006 in Levene test and p ≈ 0.0009 in Brown-Forsythe test), the non-parametric analysis with Kruskal-Wallis rank variance was used, noting the difference on the border of statistical significance (p≈0.045). The observed differences between the groups related to a slightly higher level of HbA$_{1c}$ in the normal blood flow group, compared with groups with ischemia and rigidity (HbA$_{1c}$ level difference up to 0.34%).

Table 3. HbA1c level variability in the 3 groups examined, separated according to ABI

	N	median	min.	max.	average	SD	P
<0.9	45	8.25	5.47	11.47	8.22	1.25	
0.9-1.3	199	8.35	5.47	16.50	8.77	2.16	0.045
>1.3	106	8.01	5.60	13.85	8.06	1.50	
All	350	8.18	5.47	16.50	8.48	1.91	

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DISCUSSION

The prevalence of PAD among diabetic patients is difficult to evaluate, due to common coexistence of diabetic neuropathy which may reduce the pain and other sensations in the lower limbs [14]. It varies from 9.5%-13.6% among type 2 diabetic patients [9, 14]. The most common diseases of the peripheral arteries are atherosclerosis and medial sclerosis [15].

Elevated ABI (above 1.3) is associated with high risk of arterial calcification which may cause arterial wall stiffness [8, 16]. Low ABI is a strong indicator of PAD disease among diabetic patients [15] with specifity between 88%-97%, depending of the presence, with sensitivity dropping from 100%-53% in the presence of peripheral neuropathy which may cause false negative results even in 1/3 of cases [17]. Both low and high ABI are good predictors of cardiovascular diseases, and even death [6, 7, 9, 18, 19]. Therefore, in 2003, ADA recommended measuring ABI in all diabetic patients older than 50 years of age, and in younger patients with any other PAD risk factors (e.g. smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years) [20].

In the presented study the normal ABI was present in only 45% of patients. Low ABI (below 0.9) indicates not only limb ischemia, but also increased risk of cardiac death by 67%, [9] and was present in 17.7% of admitted patients. Low ABI makes a cardiovascular event 5 times more probable than in case of ABI within the normal range [21].

In addition, among the patients admitted, 37% had elevated ABI. High ABI (> 1.4), apart from a low one, was also a predictor of cardiovascular mortality with a clear U- formation among American Indians in the Strong Heart Study [8]. Altogether, 55% of the admitted patients had abnormal ABI (both low and elevated), which represents the group of patients with elevated risk of cardiovascular death.

In the Tanno and Sobetsu Study, the brachial-ankle pulse wave velocity level, evaluated as an indicator of atherosclerotic changes, increased among the elevated plasma glucose level group, and reached statistical significance between normal glucose tolerance and both an impaired fasting glycaemia and diabetic patients [22]. Diabetes itself is a main risk factor of PAD, being more common among American Indians in the group with low and high ABI values in the Strong Heart Study [8].

A high glucose level, evaluated by the level of HbA_{1c}, is recognized as one of the major risk factors of micro-vascular complications in type 2 diabetes [10]. There was a 28% increase in the risk of PAD with every 1% increase of HbA_{1c} in UKPDS [23].

The prevalence of PAD assessed in the presented study is similar to other findings – 17.3% in the Hoorn Study [24] and 23.5% among type 2 diabetics in a community in the UK [25].

An inverse relationship was found in the current degree of diabetes control measured by HbA_{1c} level and ABI – the observed differences (HbA_{1c} level difference up to 0.34%) were found between the normal blood flow group, compared to the groups with ischemia and rigidity. There are several explanations for these findings. First of all, the group in the presented study also represent patients with diabetic polyneuropathy, which may influence the evaluation of ABI, making even 1/3 as false negative results [17]. Another explanation is that because of the totally different nature of the distribution of characteristics in this group (much greater variability and skewness), the clinical significance of this difference is questionable (Fig. 2).
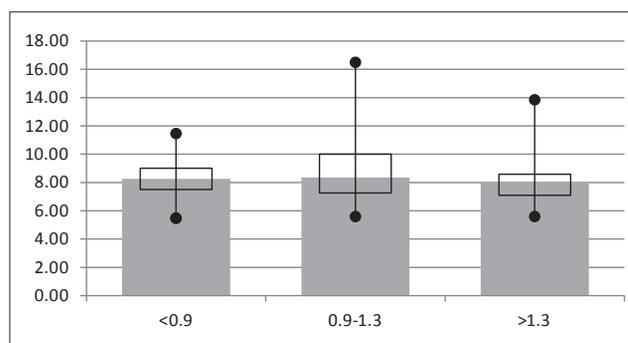

Figure 2. Distribution of HbA1c levels in ABI categories (350 measurements in 175 patients; median, bottom and upper quartiles and variance)

In other study performed in Greece, no correlation between the level of HbA_{1c} and ABI was found. However, a positive relationship between ABI and fasting glucose level and WBC (White Blood Cell count) was revealed [26]. In a National Health and Nutrition Examination Survey of 1999-2002, a correlation was found between the level of HbA_{1c} and ABI among diabetic patients, but the cut-off points for HbA_{1c} were below 7% and above 7%, with an odds ratio of 2.33 vs. 2.74 [27]. In the presented study, the mean level of HbA_{1c} was above 8%.

There is evidence of a relationship between the level of HbA_{1c} and macrovascular complications among diabetics patients. Such a connection was noticed with an increased level of HbA_{1c} – 7.9% vs 7.2% – after 6 years [23], also when pooling 3 studies in which RR of peripheral arterial disease it was associated with a 1-percentage point-higher HbA_{1c} among evaluated patients with type 2 diabetes [28].

The association between the level of HbA_{1c} and macrovascular complications needs further evaluation in clinical trials to establish the nature of such a relationship. It is especially important in the context of possible influence of HbA_{1c} reduction on the reduction of cardiovascular events among patients with long-lasting diabetes. It is also important in the context of discussion about the clinical sense of intensive glucose-lowering treatment among patients with already existing macrovascular complications, and difficulties with the reduction of plasma glucose among type 2 diabetes [10, 11].

If the patient with diabetes had no comprehensive care from the beginning, and if the patient did not achieved good results of metabolic control, especially in the early years of the disease, development of complications appears to be unavoidable, no matter how effective the treament received some years later. Consequently, it is essential that the patient with diabetes should be under specialist care from the beginning of the disease, and not at the time when chronic complications appeared, as is commonly believed. Only in this way can the patient be given the chance to avoid complications, or to slow their development.

CONCLUSIONS

1. The current degree of diabetes control has no direct impact on the diabetic angiopathy advancement evaluated as ankle-brachial index.
2. The prevalence of abnormal (low or elevated) ankle-brachial index is high and exceeds 50% among type 2 diabetic patients hospitalized due to hyperglycaemia.

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3. Because the prevalence of elevated ankle-brachial index (>1.3) is higher rather than lower (<0.9), and both are predictors of cardiovascular events, there is a need for further investigation of potential relationships between abnormal ABI and prevalence of coronary heart disease among type 2 diabetics.

REFERENCES

1. Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Fiedrichs S, Lammer J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev. 2012; 28 (Suppl. 1): 179-217.
2. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care. 1990; 13(5): 513-521.
3. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on between individuals with and without peripheral vascular disease. The EURODIAL study. Diabetologia. 2008; 51(5): 747-755.
4. Schaper NC. Lessons from Eurodiale. Diabetes Metab Res Rev. 2012; 28 (Suppl. 1): 21-26.
5. Apelqvist J, Bakker K, van Houtum WH, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007). Diabetes Metab Res Rev. 2008; 24 (Suppl. 1): 181-187.
6. Xu D, Li J, Zou L, Xu Y, Hu D, Pagodo SL, Ma Y. Sensitivity and specificity of the ankle–brachial index to diagnose peripheral artery disease: a structured review. Vasc Med. 2010; 15(5): 361-369.
7. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States. Results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004; 110(6): 738-743.
8. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality. The Strong Heart Study. Circulation. 2004; 109(6): 733-739.
9. Norman P E, Davis W A, Bruce D G, Davis T M E. Peripheral arterial disease and risk of cardiac death in type 2 diabetes. The Fremantle Diabetes Study. Diabetes Care. 2006; 29(3): 575-580.
10. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352(9131): 837-853.
11. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009; 360(2): 129-139.
12. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. The Action to Control Cardiovascular Risk in Diabetes Study Group: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358(24): 2545-2559.
13. Charuruks N, Milintagas A, Watanaboonyoungcharoen P, Ariyaboonsiri C. Determination of reference intervals of HbA1C (DCCT/NGSP) and HbA1C (IFCC) in adults. J Med Assoc Thai. 2005; 88(6): 810-816.
14. Gregg EW, Sorlie P, Paulose-Ram R, Gu Q, Eberhardt MS, Wolz M, et al. Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey. Diabetes Care. 2004; 27(7): 1591-1597.
15. Schaper NC, Andros G, Apelqvist J, Bakker K, Lammer J, Lepantalo M, et al. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev. 2012; 28 (Suppl.1): 218-224.
16. Reaven PD, Sacks J. Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. Diabetologia. 2005; 48(2): 379-385.
17. Williams DT, Harding KG, Price P. An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care. 2005; 28(9): 2206-2210.
18. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis. 1991; 87(2-3): 119-128.
19. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Rouckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ. 1996; 313(7070): 1440-1444.
20. American Diabetes Association: Peripheral arterial disease in people with diabetes. Diabetes Care. 2003; 26(12): 3333-3341.
21. Ogren M, Hedblad B, Engstrom G, Janzon L. Prevalence and prognostic significance of asymptomatic peripheral arterial disease in 68-year-old men with diabetes. Eur J Vasc Endovasc Surg. 2005; 29(2): 182-189.
22. Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, et al. Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose. The Tanno and Sobetsu Study. Diabetes Care. 2003; 26(2): 437-440.
23. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: Hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care. 2002; 25(5): 894-899.
24. Beks PJ, Mackaay AJ, de Neeling JN, de Vries H, Bouter LM, Heine RJ. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. Diabetologia. 1995; 38(1): 86-96.
25. Walters DP, Gatling W, Mullee MA, Hill RD. The prevalence, detection, and epidemiological correlates of peripheral vascular disease: a comparison of diabetic and non-diabetic subjects in an English community. Diabet Med. 1992; 9(8): 710-715.
26. Papazafiropoulou A, Kardara M, Sotiropoulos A, Bousboulas S, Stamataki P, Pappas S. Plasma glucose levels and white blood cell count are related with ankle brachial index in type 2 diabetic subjects. Hellenic J Cardiol. 2010; 51(5): 402-406.
27. Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. Diabetes Care. 2005; 28(8): 1981-1987.
28. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004; 141(6): 421-431.