Turkish Journal of Endocrinology and Metabolism, (2000) 1 : 15-18

ORIGINAL ARTICLE

Medial Arterial Calcification is a Predictor of Cardiac Autonomic Neuropathy in Diabetic Patients

Ayşin Öge* **Serap Demir**** **Osman Müftüoğlu****

* *Adnan Menderes University, School of Medicine Department of Internal Medicine, Aydın*

** *Ankara Numune Hospital, Department of Internal Medicine, Ankara*

Medial arterial calcification (MAC) is one of the complications of diabetes mellitus and recently, a relationship between cardiac autonomic neuropathy and MAC has been pointed out. By means of this relationship, we evaluated whether MAC may be important in the detection of cardiac morbidity. A total of 100 diabetic patients (33 Type 1 and 67 Type 2) and 50 healthy subjects were included in this study. We aimed to show a correlation between autonomic nepopathy, cardiac morbidity and MAC, and also investigated whether MAC is a predictor of cardiac mortality or not. Orthostatic systolic blood pressure change, respiratory cardiac rate change and conduction velocity (by calculating the QTc duration of each subject according to Bazzet formula) were all calculated. Of the diabetic patients, 28% had cardiac autonomic neuropathy. In 70% of diabetic patients with MAC, the orthostatic blood pressure change was significatly greater, the cardiac rate change with deep inspiration was lower, and the QTc duration was longer in comparison with diabetic patients without MAC. The relationship beween MAC and diabetic cardiovascular autonomic neuropathy was statistically significant ($p<0.05$). There was also a significant correlation between diabetic cardiovascular autonomic neuropathy (QTc duration) and the duration of diabetes. The mean duration of diabetes in patients with long and normal QTc was 13 ± 5.4 and 5 ± 5.2 years, respectively. In conclusion, we recommend that MAC can be an predictor for cardiac autonomic neuropathy and play a role in the prevention of diabetic cardiac mortality. If more extensive studies confirm our data, then clinical practice can be altered.

Key words: Diabetes mellitus, medial arterial calcification, autonomic neuropathy

Introduction

Diabetes Mellitus consists of etiologically and clinically heterogeneous hyperglycemic disorders (1). Epidemiologic data have long demonstrated a correlation between diabetes mellitus and cardiovascular disease. This correlation holds true particularly for ischemic heart disease, in which the data for patients with diabetes show that such patients have more coronary artery disease, acute ischemic complications and higher mortality rates (2-5).

Diabetic patients with lower extremity arterial disease are at on increased risk of having coronary artery disease (CAD) (6-9). The concomitant presence of CAD with lower extremity arterial disease is important as CAD is the leading cause of morbidity and death among individuals with extremity arterial disease. Medial arterial calcification (MAC) which results from calcium deposition in tunica media of medium sized arteries (10-12) is seen more frequently in diabetics with complications than in ones without complications (13).

Correspondence address:

Ayşin Öge
Adnan Menderes Üniversitesi Tıp Fakültesi,
İç Hastalıkları Ana Bilim Dalı
09100 Aydın, Turkey
Phone: 90 256 213 22 70
Fax: 90 256 212 01 46
e-mail: ayoge@hotmail.com

MAC has been well established especially in diabetic with autonomic neuropathy (14).

Since the involvement of the autonomic nervous systems indicates a poor prognosis, early detection and subsequent management are important (15). Recently, the relationship between MAC and cardiac autonomic neuropathy has been under investigation (14). Cardiovascular mortality was shown to be increased in diabetic patients with MAC (16-17) and accepted as an independent marker of mortality for diabetics (18). If a patient presents MAC, she have a mortality risk 1,5 times, amputation risk 5,5 times and coronary artery disease risk 1,6 times greater than diabetics without MAC (16). Due to the relationship between MAC and autonomic neuropathy or cardiovascular mortality, MAC can be accepted as a predictor of cardiovascular mortality. From this point of view, patients with MAC should be examined regularly. The purpose of this study was to evaluate the relationship between MAC and cardiac autonomic neuropathy.

Materials and Methods

Thirty three type 1 (12 females and 21 males; age, 27,2±9 yrs; HbAıc: 7,2±2 %, duration of diabetes: 10,4±3 yrs.), 67 Type 2 (46 females and 21 males; 52,4±8 yrs; HbAıc: 8±2,8 %; duration of diabetes: 7,4±4 yrs.) diabetic patients and 50 healthy were included in this study. The diabetic patients and normal subjects were age and sex matched. MAC was assessed by antero-posterior and lateral foot and antero-posterior knee X-rays. We calcutated orthostatic systolic blood pressure change, respiratory cardiac rate change and conduction velocity (by calculating the QTc duration of each subject according to Bazzet formula) for diagnosis of cardiac autonomic neuropathy. QTc was calculated by Bazzet formula, QTc=QT (seconds) /√ RR. Normal range of QTC was accepted as between 330-440 miliseconds, durations above 440 miliseconds were accepted as pathologic.

Each patient was also examined for postural hypotension. Blood pressre was measured while the subject was lying down and again 1 min after standing up, and the difference in sytolic blood pressure was noted. Blood pressure response to standing up (fall in systolic blood pressur) was accepted as normal: ≤ 10 mmHg. borderline: 11-29 mmHg, abnormal ≥ 30 mmHg.

Heart rate response to deep breathing was conveniently performed by asking the patient to sit quietly and then breathe deeply and evenly at six breaths/min (i.e.5s in and 5s out). the maximum and minimum heart rates during each 10 s breathing cycle were calculated from R-R intervals recorded by electrocardiogram. The mean of the differences during three successive breathing cycles gave the "maximum-minumum heart rate". The test of heart rate response to deep breathing as assessed and normal 0 ≥ 15 beats/min, borderline: 11-14 beats/min, abnormal : ≤ 10 beats/min. Data from the study groups were analyzed using Student's test and Mann-Whitney U test.

Results

Of the diabetics, 29% were found to have long QTc time and 25% had postural hypotension. Among the patient with cardiovascular autonomic neuropathy, 28% had MAC and 70% of patients with MAC had long QTc time and lower cardiac rate change with deep inspiration and postural hypontension. The relationship of MAC with QTc time and cardiovascular neuropathy was statistically significant ($p<0.05$). Table 1. shows the relationship between MAC and Diabetic Cardiovascular Autonomic Neuropathy (DCAN).

Table 1. Relationship between MAC and diabetic cardiovascular autonomic neuropathy (DCAN).

	MAC (-)		MAC (+)		Results	
	n	%	n	%	n	%
DCAN (-)	72	80	3	30	75	75
DCAN (+)	18	20	7	70	25	25
Results	90	90	10	10	100	100

$p < 0.05$

Diabetic patients with MAC had longer QTc time lower heart rate change with deep inspiration and lower/higher postural hypotension when compared with the diabetics without MAC ($p<0.05$). While 28% of diabetics had cardiovascular autonomic neuropathy, none of the control group were observed to have abnormal measurements related to cardiovascular autonomic neuropathy ($p<0.005$). Table 2. summarizes the results of cardiovascular autonomic neuropathy tests in diabetics with and

without MAC. The mean duration of disease in patients with long QTc was 13 ± 5.4 years and was 5 ± 5.2 years in patients with normal QTc (p=0.0003). Figure 1. Demonstrates the QTc time according to the duration of diabetes.

Table 2. Comparison of diabetic patients with and without MAC according to the measurements of cardiovasclar autonomic neuropathy tests.

Test	Diabetic patients MAC (+) n=10	MAC (-) n=90	Controls n=50
Posturalhypotension	30±10 mmHg	22±10 mmHg	6 ± 5 mmHg
Heart rate change with deep inspiration	18±5 beats/min	12±5 bear/min	5±4 beats/min
QTc time	495±10 msn	460±12 msn	335±30 msn

p<0.05

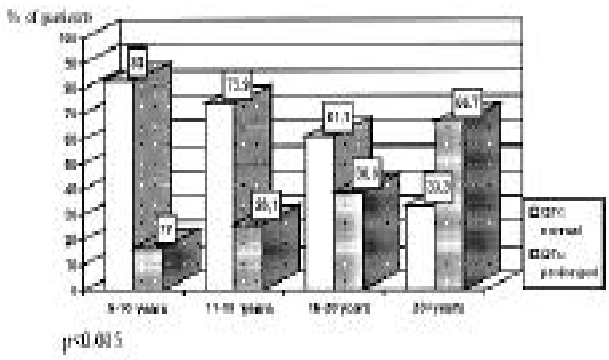

Figure 1. Relationspin between QTc time and duration of diabetes.

Discussion

There are many reports about neuropathy being important in the ethiopathogenesis of MAC (17-19), which is seen more commonly in diabetics (13-20-22). MAC is prominent especially in diabetic patients with neuropathy (13-16-23). Edmonds et. al. reported that MAC was more prevalent in diabetic patients with neuropathy and especially autonomic neuropathy was important in the pathogenesis (17).

MAC is accepted as a complication of diabetes and its relationship with other chronic complication has been investigated in many studies (16, 22-24). The correlation between MAC and increased cardiovascular mortality has been proved (17-25) and MAC is an accepted marker of mortality in diabetics (16-26). Another important aspect of MAC is the relationship with autonomic neuropathy and cardiovascular autonomic neuropathy.

Arterial calcification first starts in the atrophic smooth muscles (10). In animal models, it was shown that atrophy and fragmentation of smooth muscle cells resulted from the impairment of autonomic innervation with time (27-28). At advanced ages the autonomic supply of smooth muscles decreases (28) and in cases with sympatectomy, necrotic areas are seen in model smooth muscles due to decreased autonomic supply (27). These cases indicate the importance of early detection of MAC; because MAC and autonomic neuropathy are closely related and diabetics with MAC have 1,5 times higher mortality and 1,6 times higher risk of coronary heart disease than diabetics without MAC (16-23).

Of our patients, 28% of the diabetics were found to have cardiovascular autonomic neuropathy and 70% of paitents with MAC had cardiovascular autonomic neuropathy. The relationship between MAC and autonomic neuropathy was statistically significant. Although 29% of patients had a long QTc duration, this rate was 70% in paients with MAC. The relationship between MAC and QTc duration was statistically significant.

As result, we concluded that if patients with MAC also have autonomic neuropathy, the risk of mortality should be thought of as signifcantly increased and such cases should be in a closer follow-up policy. Hence, many patients with a higher risk of cardiac mortality can be detected earlier and subsequently treatment will decrease the mortality rate in this poputation.

References

1. Akalın S. Diabetes Mellitusun Kliniği. Modern Tıp Seminer 1989. Ed: Gedik O, Akalın S: 1-12.
2. Standl E, Janka HU. Der Diabetsche FuB. In: Mehneyt H, Schöffling K (Hrsg.): Diabetologie in Klinik und Praxis, Thieme, Suttgart 2 Aufl: 513-528, 1984.
3. Panzram G. Mortality and survival in type 2 (non-insulin dependent) diabetes mellitus. *Diabetologia* **30:** 123-131, 1923.
4. Jarrett RJ. The epidemiology of coronary heart disease and related factors in the context of diabetes mellitus and impaired glucose tolerance. In: Jarrett RJ- ed. Diabetes

and Heart Disease. Amsterdam: Elsevier Science Publis-her **BV: 1-23,** 1984.

5. McGuire DK, Granger CB. Diabetes and ischemic heart disease. *Am Heart J* **138:** S 366-375, 1999.
6. Hertzer NR, Young JR, Beven EG, O'Hara PJ, Graor RA, Ruschhaupt WF, et al. Late results of coronary bypass in patients presenting with lower extremity ischemia: The Cleveland Clinic Study. *Ann Vasc Surg* **1:** 411-9, 1987.
7. DeBakey M, Lawrie GM, Glaeser DH. Patterns of athero-sclerosis and their surgical significance. *Ann Surg* **201:** 115-31, 1985.
8. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* **30:** 50-7, 1989.
9. Orchard TJ, Stranddness DE. Assessment of peripheral vascular disease in diabetics. *Circulation* **88:** 819-28, 1993.
10. Morgan AJ. Mineralized deposits in the thoracic aorta of aged rats: ultrastructural and electron probe x-ray micro-analysis study. *Exp Gerontol* **5:** 563-73, 1980.
11. Bevan RD. Effect of sympathetic denervation on smooth muscle cell proliferation in the growing rabbit ear artery. *Circulation Res* **37:** 14-19, 1975.
12. Bevan RD, Tsuru H: Long-term denervation of vascular smooth muscle causes not only functional but structural chages. *Blood Vessels* **16:** 109-112, 1979.
13. Young MJ. Adams Je, Anderson GE, Boulton AJM, Cavanag PR. Medial arterial calcification in the feet of the diabetics patients and matched non-diabetic control subjects. *Diabetologia* **36:** 615-621, 1993.
14. Cronin CC, O'Sullivan DJ, Mitchell TH. Medial arteriad calcification, calcific aortic stenosis and mitral annular calcification in a diabetic patient with severe autonomic neuropathy. *Diabet Med Aug* **13(8):** 768-70, 1996.
15. Matsuto S. Assessment of diabetic cardiovascular auto-nomic neuropathy by heart rate variability and pulse wave velocity. *Rinsho Byori Oct* **46(10):** 1037-42, 1998.
16. Everhart JE, Pettitt DJ, Knowler WC, Rose FA and Bennett PH. Medial arterial calcification and its associa-tion with mortality and complications of diabetes. *Diabetologia* **31:** 16-23, 1988.
17. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A and-Deckert T. Coronary heart disease in young type 1 (insulin-dependent) diabetic patient with and without diabetic nephropathy: İncidence and Risk Factors. *Diabetologia* **30:** 144- 148, 1987.
18. Bowen BD, Koenig EC, Viele A. A study of the lower extremities in diabetes as compared with non-diabetics states from the standpoint of X-ray findings, with particular reference ta the relationship of arterio-sclerosis and diabetes. *Bulletin of the Buffalo General hospital*. **2:** 35-41, 1924.
19. Lithner F, Hietala SO and Steen L. Skeletal lesion and arterial calcifications of the feet in Diabetics Acta Med. *Scand (Suppl)* **47:** 687, 1984.
20. Neubauer B. A quantitative study of peripheral arterial calcification and glucose tolerance in elderly diabetics and non-diabetics. *Diabetologia* **7:** 409-413, 1971.
21. Morrison LB, Bogan IK. Calcification of the vessels in diabetes. *Jama* **92:** 11424-1426, 1929.
22. Goebel FD and Füessl HS. Mönckeberg's sclerosis after sympathetic denervation in diabetic and non-diabetic subjects. *Diabetologia* **24:** 347-350, 1983.
23. Edmonds ME, Morrison N, Laws JW, Watkins PJ. Medial arterial calcifcation and diabetic neuropathy. *British Medical Journal Volume 27 March* **284:** 928-930, 1982.
24. Young RJ Macintyre CCA, Martyn CN, Precoot RJ, Smith AF, Vibeti G, Clarke BF. Progression of subclinical polyneuropathy in young patients with type 1 (Insulin-dependent) diabetes, associations ith glycemic control and micro angiopathy (microvascular complications) *Diabetologia* **29:** 156-161, 1986.
25. Lachman AS, Spray TL, Kervin DM, Shugall GI, Roberts WC. Medial calcinosis of Mönckeberg. *The American Journal of Medicine October Volume* **63:** 615-622, 1977.
26. Young MJ, Boulton AJ, Macleod AE, Williams DR and Sanksen PH. Amulticentre study of the prevalance of diabetics peripheral neuropathy in the United Kingdom Hospital Clinic Population. *Diabetologia* **36:** 150-154, 1993.
27. Kerper AH, Collier WD. Pathological changes in arteries following partial denervation. *Proc Soc Exp Biol Med* **24:** 493-494, 1926.
28. Botar J. The autonomic nervous system. *Budopest: Akademid Kiado* 1996.