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ORIGINAL PAPER

Mortality After Acute Myocardial Infarction: Significance of Cardiovascular Diabetic Autonomic Neuropathy (CDAN)

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The aim of this study was to compare intrahospital and long-term mortalities after more than 10 years of the follow up after the first acute myocardial infarction (AMI) with patients with and without CDAN and without diabetes mellitus (DM). **Methods:** The study was based on 76 (43 men and 33 women) with DM type 2, CDAN was detected in 51 patients, and 374 (295 men and 79 women) without DM consecutively hospitalized with the first-ever AMI from January 1998. to December 2000. in Clinical Center of Montenegro Podgorica. Patients were followed until December 31. 2011. CDAN was searched for by standardized five tests evaluating heart rate and blood pressure variations. **Results:** Intrahospital mortality was presented in 10. 53 % diabetic patients and 5. 61 % nondiabetic patients, this difference is significant (p=0.048). Long-term mortality was presented at 24 (82. 75%) patients with CDAN and 5 (17. 25%) patients without CDAN (p=0.029). Long term mortality rate was significantly higher in diabetic patients 29 (42. 64 %) than in nondiabetic patients 102 (30. 72 %) (p=0.012). **Conclusion:** Intrahospital mortality was significantly higher in diabetic than in nondiabetic patients. Identically the mortality after more than 10 years of the follow up after the first AMI was significantly higher in diabetic with, than in diabetic patients without CDAN, as in diabetic than in nondiabetic patients. Key words: Myocardial infarction, Mortality, Diabetes mellitus, Cardiovascular diabetic autonomic neuropathy.

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1. INTRODUCTION

It is well established that patients with diabetes mellitus (DM) have a higher short-term mortality after acute myocardial infarction (AIM) than patients without DM. Several recent studies have found that hospital, 28-day and 1-year mortality after AMI was approximately 1.5–2 times higher in diabetic patients (1-3). As it is known that most patients survive beyond this period, it is important to study the difference in long-term survival after an AMI between diabetic and nondiabetic patients as well. Survival after an AMI may be particularly worsened beyond the poorer prognosis already conferred by the presence of DM itself, as diabetic patients with an AMI may experience more severe coronary heart disease and more complications (left ventricular dysfunction and heart failure, significant ventricular arrhythmias) than nondiabetic patients with an AMI (2, 3). There are relatively few recent studies that address differences in long-term prognosis after an AMI between diabetic and nondiabetic patients with follow-up lasting through the second half of the 1990s (4-8). Moreover, data largely originate from clinical trials or single centers (4, 5, 7). Several studies reported that DM is independently associated with long-term mortality (4-9) CAN is a common form of diabetic autonomic neuropathy and causes abnormalities in heart rate control as well as central and peripheral vascular dynamics. The clinical manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension, painless myocardial ischemia, and increased risk of mortality. CAN contribute to morbidity, mortality, and reduced quality of life for persons with diabetes. (10) Mortality rates after a myocardial infarction are also higher for diabetic patients than for nondiabetic patients.(11) This may be due to autonomic insufficiency, increasing the tendency for development of ventricular arrhythmia and cardiovascular events after infarction.

The aim of this study was to compare intrahospital and long-term mortalities after more than 10 years of the follow up after the first acute myocardial infarction with patients with and without CDAN and without diabetes mellitus. Secondary aim was to study the interaction between treatment and diabetes on the long- term mortality rate.

2. METHODS

The study was based on 450 consecutive patients hospitalized with a first-ever AMI from January 1998. to December 2000. in Clinical Center of Montenegro Podgorica. The diagnosis of the heart attack is based on your symptoms, ECG and the results of your blood studies. Blood may be drawn to measure levels of biochemical markers. A total of 76 patients (43 men and 33 women), years of age 64, 08±9, 06 with DM type 2, CDAN was detected in 51 patients, and 374 (295 men and 79 women) years of age 56, 05 ± 10, 77 without DM. The diagnosis of diabetes mellitus was based on medical records or diabetes diagnosed during the event. (Table 1.)

Diabetic patients were older compared to nondiabetic patients. The other known causes of CDAN (uremia, alcoholism, amyloidosis, Landry-Gullian Barre syndrome) were excluded. All factors that could influence the test results were excluded before tests were performed. We used a standard battery of cardiovascular autonomic function tests to assess all diabetic patients: the heart rate responses to the Valsalva manoeuvre, standing up and deep breathing; and the blood pressure responses to standing up and sustained handgrip. (12) In brief, autonomic involvement was categorised as normal (all tests normal), early (one heart rate test abnormal), definite (two or more heart rate tests abnormal), severe (abnormal heart rate tests plus one or both blood pressure tests abnormal), or atypical (any other combination of abnormalities).(13) Patients were followed until December 31. 2011. The endpoint study was death from any cause.

Characteristics		Group A		Group B		p
		N	%	N	%	
Total		76	100	374	100	
Age	X	64,08		56,05		< 0,01
	SD	9,06		10,77		
	Min-Max	46 – 81		36–78		>0,05
Smokers		28	36. 8	206	55. 0	>0,05
BMI* >25		53	69. 7	274	73. 2	>0,05
Hypertension		50	65. 8	225	60. 2	>0,05

Table 1. Characteristics of first acute myocardial infarction patients with and without diabetes mellitus Group A diabetic patients.. Group B nondiabetic patients. BMI* Body mass index

Characteristics		Group A		Group B		The level of significance
(N / %)		N(m/f)	%	N(m/f)	%	
Total		76	100	374	100	x2=2,527 p=0,048
Mortality	Yes	8(5/3)	10,53	21(16/5)	5,61	
	No	68	89,47	353	94,69	

Table 2. Intrahospital mortality in diabetic and non diabetic patients after acute myocardial infarction

Statistics. The patients were separated into three cohorts representing as diabetics with CDAN, without CDAN and nondiabetics. We used statistics and analytics software package STATISTICA. The level of significance is . P value is denoted by. Of course, the null hypothesis is rejected in a case We apply the test based on the normal approximation to the binomial and the Fisher-Irwin test. The null hypothesis is, where and are relative frequency of mortality in the first and the second group respectively. The alternative hypothesis is

3. RESULTS

Between 1. January 1998. and 31. December 2000. 43 men and 33 women in the age group 46 through 81 years with DM type 2, and 295 men and 79 women the age group 36 through 78 years without DM had a first ever AIM. Cardiovascular risk factors dyslipidemia, hypertension, smoking, central obesity were presented at diabetic patients with and without CDAN and nondiabetic patients at the same percent. (P> 0.05) (Table 1.) At onset of the first AIM, 22, 4 % were patients with newly diagnosed type 2 diabetes,

67, 1% were treated with oral glucose lowering agents, 3, 9 % with insulin, 2, 6% with oral glucose lowering agents and insulin, 4, 0 % with diet only. During the hospitalisation 33, 82 % were treated with insulin. These change was statistically significant regarding admission in coronary unit. We showed intrahospital mortality in patients with and without diabetes mellitus. (Table 2.)

Intrahospital mortality was presented in 10.53% diabetic patients and 5.61 % nondiabetic patients, this difference is significant (p =0. 048). Cause of death in diabetic and non diabetic patients was ventricular fibrilation.

After more than ten years of the follow up in diabetic group 29 patients (m/f 18/11) died and in nondiabetic group 102 (m/f 72/30). We found that frequency of mortality were sig-

Treatment	Mortality%	P
metformin+insulin vs sulfonylurea + metformin	7,7 vs 42,9	0,0103
metformin + insulin vs sulfonylurea +i nsulin	7,7 vs 66,7	≈0
metformin + insulin vs sulfonylurea	7,7 vs 93,8	≈0
sulfonylurea + metformin vs sulfonylurea + insulin	42,9 vs 66,7	0,0328
sulfonylurea + metformin vs sulfonylurea	42,9 vs 93,8	≈0
sulfonylurea + insulin vs sulfonylurea	66,7 vs 93,8	≈0

Table 3. Mortality rate in diabetic patients according to antidiabetic treatment

Mortality	CDAN No (%)	NON CDAN No(%)
VF+AIM	7 (29%)	2 (40%)
STROKE	6 (25%)	1 (20%)
COMA+GAN	2 (8%)	1 (20%)
RF	2 (8%)	0
HF	3 (13%)	1 (20%)
HYPO	1 (4%)	0
SUDD D	3 (13%)	0
Total	24 (100%)	5 (100%)

Table 4. Causes of death after more than 10 years in diabetic patients with and without CDAN

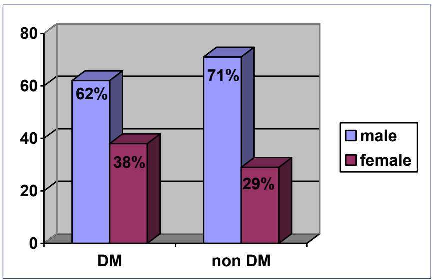

Figure 1. Distribution of mortality by gender

nificantly different between diabetic patients with CDAN and diabetic patients without CDAN (p=0. 029). The severity of CDAN did not influence the frequency of mortality in diabetic patients (p=0. 5). This study could not found significant difference in mortality of diabetic patients in response the gender (p=0. 207), indicating that risks are equally elevated among men and women.

We have analyzed effect of treatment on mortality in diabetic patients. The patients were treated with different combination of drugs to control diabetes. (Table 3.)

Patients who were treated with combination of insulin and metformin had the best survival.

There was a significant difference between mortality rate in men and women in group of nondiabetic patients (p=0. 0064) during of the follow up. Mortality was higher in women than in men after more than 10 years of the follow up after the first AMI. That difference was not found during hospitalisation for the first AMI. The difference in mortality was present between nondiabetc and diabetic patients (p=0. 012) after more than ten years of the follow up.

Causes of death after more than 10 years of the follow up after the first acute myocardial infarction (AMI) in diabetic patients are shown in Table 4.

Ventricular fibrilation was the most frequently cause of death in diabetic patients with and without CDAN and non diabetic patients during hospitalisation and after 10 years of the follow up after the first AIM.

Gender distribution of death between diabetic and nondiabetic patients after more than 10 years of the folllow up is showen on graf 1.

4. DISCUSSION

Diabetic patients have a high rate of coronary heart disease, which may be asymptomatic owing to autonomic neuropathy. Silent ischemia is significantly more frequent in patients with than in those without autonomic neuropathy (38% versus 5%). The cause of silent myocardial ischemia in diabetic patients is controversial. It is clear, however, that a reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction and thereby delay appropriate therapy. In nondiabetic patients, acute myocardial infarction has a circadian variation with a significant morning peak. The characteristic diurnal variation in the onset of myocardial infarction is altered in diabetic patients, with a lower morning peak and a higher percentage of infarction during evening hours. The blunted morning surge of incidence of myocardial infarction results from altered sympathovagal balance in patients with cardiac autonomic neuropathy.(14, 15)The results of the Diabetes Control and Complications Trial clearly showed that intensive glycemic treatment can prevent the development of abnormal heart rate variation and slow the deterioration of autonomic dysfunction over time for individuals with type 1 diabetes (16). For individuals with type 2 diabetes, intensive multifactorial treatment slowed the progression of autonomic neuropathy in one study (17), whereas in another study those in the intensely treated group showed a small tendency for improved autonomic function, with deterioration noted in the conventionally treated group (18). Our results showed that diabetic patients were treated with metformin and insulin had the best survival. Recently, it was demonstrated that overweight type 2 diabetic patients had metformin related decreases in free fatty acids and insulin resistance that were associated with improved sympatovagal balance. (19). In another study patients treated with insulin had the worst short and long–term prognosis after AIM in both gender. (20)

In the Cooperative Cardiovascular Project, post AIM diabetic patients treated with beta blockers had a 36% reduction in mortality. (21) Our study presented that 19, 6 % diabetic patients with CDAN, 55% without CDAN and 60, 5% nondiabetic patients treated with beta blockers, difference is significant. Beta blockers that are cardioselective or lipophilic might modulate the effects of autonomic dysfunction in diabetes mellitus either centrally or peripherally by opposing the sympathetic stimulus and thereby restore the parasympathetic-sympathetic balance.(22) Results from different studies regarding differences in mortality between diabetic and non-diabetic patients are conflicting. Oppositely with our findings, it has been reported that DM has no independent predictive value on short-term mortality (23) Yet, several other recent studies as our study showed that short-term (<1 year) mortality after AMI was significantly higher (approximately 1.5 to 2 times) in diabetic patients compared with nondiabetic patients (1-3, 24). Weitzman et al. (25) found a significant higher 1-year mortality in diabetic men (odds ratio (OR) 1.5; 95% CI 1.2–1.9), but no significant association in women. Recent studies regarding differences in long-term mortality (follow-up ranging from 4 to 10 years) after AMI showed an approximately 1.5–2.5 higher risk of dying in diabetic patients (4-8, 26]. Ishihara et al. (27) showed that DM was an independent predictor of 10-year mortality in patients with single vessel disease (OR 1.81; 95% CI 1.27–2.54), but in patients with multivessel disease the influence of DM was nonsignificant (OR 1.17; 95% CI 0.85–1.60). Melchior et al.(5) reported that the difference in mortality after AMI between diabetic and non-diabetic patients increased with time (relative risk ranging from 1.03 (95% CI 0.81–1.31) at 30 days to 1.43 (95% 1.24–1.66) at 2 months-3 years and 1.74 (95% CI 1.36–2.23) at 7–9 years in patients admitted between 1990 and 1992).We found no significant differences in short and long-term mortality after the first AMI between men and women in diabetic patients. A few other studies examined gender differences in mortality after an AMI in diabetic patients. Crowley et al. (28) found that women with DM were at increased risk of hospital death compared to men (OR 1.37; 95% CI 1.08–1.75), but no significant gender difference in 1-year mortality (HR 1.25; 95% CI 0.99–1.58) and 10-year mortality (hazard ratio 1.00; 95% 0.99–1.58) was found. Two other studies showed a higher short-term (hospital or 28-day) mortality in women (2, 29).The higher risk of long-term mortality in first AMI patients with DM reinforces the importance of vigorous preventive measures by lifestyle advice and drugs in these patients. Currently, achievement of lifestyle and risk factor goals for reducing mortality in diabetic patients with AMI is poor, as illustrated by Pyorala et al. (30) who reported that 20% of diabetic patients continued to smoke, 43% were obese, 57% had hypertension and 55% had hypercholesterolemia at least 6 months after hospitalization for coronary heart disease. A long-term, intensive approach consisting of behavior modification and pharmacologic therapy aimed at multiple risk factors is necessary, as it has been shown that this results in an impressive reduction in cardiovascular complications in patients with DM (9, 31).

5. CONCLUSION

Our findings in an unselected cohort covering a complete nation show that diabetic patients especially with CDAN are at an increased risk of long-term mortality after the first acute myocardial infarction. Yet, there are no significant differences in short-term mortality. Risks appear to be equally elevated in men and women. These results stress the importance of secondary prevention by lifestyle advice and drugs in diabetic patients after the first AMI. Future studies should evaluate whether early identification of diabetic patients with CDAN and an intense treatment before, during and after AIM can lead to a reduction in mortality. Our study showed that regional myocardial autonomic denervation and altered vascular responsiveness in diabetic autonomic neuropathy may predispose to malignant arrhythmogenesis and sudden cardiac death, that treatment with beta blockers should be encouraged.

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