ORIGINAL ARTICLE

CIRCADIAN VARIATION IN THE ONSET OF ACUTE MYOCARDIAL INFARCTION IN DIABETICS

Suresh Kumar, Naresh Kumar*, Haresh Kumar*, Rizwan Ahmed Niazi, Muhammad Farhan Rashid

Endocrinology Department Services Hospital, Lahore, *Cardiology Department, Shalamar Hospital Lahore-Pakistan

Background: It has been shown in previous studies there is circadian variation in the onset of acute myocardial infarction. The objective of this study was to evaluate the relation of circadian variation in onset of Acute Myocardial infarction in Diabetic subjects. **Methods**: This study was conducted at the Services Institute of Medical Sciences Lahore and Punjab Institute of Cardiology from January 2015 to February 2016. Hundred diabetic and 100 Non-diabetic patients with Myocardial infarction were included in the study. Among diabetics those were included in the study that had diabetes for ≥5 years. The time of onset of symptoms to determine the circadian rhythm was noted. In order to determine the frequency of acute myocardial infarction associated with circadian rhythm, 24 hours of the day were divided into four equal sections of 6 hours each. We noted time of onset of acute MI. Thereafter, patients were bracketed in their respective six-hour time periods. These six-hour periods were 0–6, 6:01–12, 12:01–18, and 18:01–24 hours. **Result:** In this study patients' mean age was 59.16±13.81. Forty-two (71.2%) non-diabetic patients had acute myocardial infarction (AMI) during 6:00–12:00 hours whereas 17 (28.8%) diabetic patients presented with AMI during this time. **Conclusion**: Incidence of AMI is significantly increased in the morning 6:01–12:00 hours in non-diabetics. However, diabetic subjects did not show significant increased incidence of AMI during this time rather there was increased incidence of AMI during 0–6:00 hours.

Keywords: Circadian variation; Myocardial infarction; Diabetes

Citation: Kumar S, Kumar N, Kumar H, Niazi RA, Rashid MF. Circadian variation in the onset of acute myocardial infarction in diabetics. J Ayub Med Coll Abbottabad 2017;30(1):71–3.

INTRODUCTION

Cardiovascular disease (CVD) has become the commonest cause of mortality, accounting approximately 30 percent of deaths worldwide.[1] Approximately 50 percent of the cases of CVD occur in Asia.[2] Cardiovascular disease remains the main cause of morbidity and mortality worldwide.[1–3] There has been considerable interest in finding the underlying mechanisms responsible for the occurrence of Acute Myocardial Infarction (AMI) in last 3 decades.[4]

Stroke, AMI and cardiac arrhythmias, contradictory to earlier beliefs do not occur randomly over the day and night but rather cluster into an early morning peak.[5] Even though, there are contradictory reports regarding circadian rhythm in the onset of AMI amongst diabetics[6,7], Zarisch *et. al.* demonstrated that morning peak of ischemia was not experienced by the patients with moderate to severe autonomic nervous system dysfunction.[8]

Poor control of blood sugar in diabetics or long-standing diabetes is often associated with autonomic neuropathy. Marked attenuation of the morning peak was observed in type 1 and type 2 diabetics of ≥5 years duration. Type 2 diabetic patients of less than 5 years duration had the same pattern of circadian rhythm of acute MI as of non-diabetic patients.[9] The current study was undertaken to determine whether presence of diabetes can change the time of onset of myocardial infarction in this part of the world.

MATERIAL AND METHODS

This study was conducted at Services Hospital Lahore and Punjab Institute of Cardiology from January 2015 to February 2016. Patients admitted in General Medicine wards and Cardiac Care Units (CCU) of the hospitals between the study periods were included in the study. The study was powered for 200 patients by taking 10% confidence interval and 80% power of the test using population proportion of the circadian variation in the onset of acute myocardial infarction in diabetics as compared to non-diabetics (32% vs 44%). The time of onset of symptoms to determine the circadian variation was noted. In order to determine the frequency of AMI associated with circadian rhythm, 24 hours of the day were divided into four equal sections of 6 hours each. We noted time of onset of AMI. Thereafter, patients were bracketed in their respective six-hour time periods. These six-hour periods were 0–6, 6:01–12, 12:01–18, and 18:01–24 hours. Start of symptoms was considered as time of onset. Non-probability consecutive sampling technique was used to select the patients. 100 Patients with Diabetes Mellitus for ≥5 years (with HbA1c >7%) and 100 patients without DM age between 20–90 years of both genders admitted to CCU with AMI between the study periods were included in the study. Patients with

diagnosed hypertension, renal dysfunction (Creatinine >3.0 mg/dl) and hepatic dysfunction (Aminotransferases more than twice normal or raised bilirubin >1.2 mg/dl) were excluded from study. Acute Myocardial Infarction was confirmed by ECG and raised Cardiac markers. We established the duration of diabetes from either the medical records or patients were inquired about the duration in case where the records were not available. Baseline characteristics such as age, medical history, investigation, treatment history and medication use were recorded. Patient reported time of beginning of discomfort was used as onset time of beginning of AMI.

RESULTS

The mean age of the subjects included in this study was 59.16±13.81 (range 29–90 years). One hundred and twenty-nine (64.5%) were male cases while 71 (35.5%) were female cases who were selected. No significant demographic difference in the study and controlled group was noted (Table-1). There was a significant difference between circadian patterns on onset of MI symptoms in non-diabetic group (71.2%) as compared to diabetic patients (28.8%) (*p*-value 0.001 table-2). We observed double peak on the onset of symptoms, first during 6:01–12:00 hours in 42 (71.2%) patients and the second between 12:01–18:00 hours in 25 (52.1%) in non-diabetics (Table-2). However, diabetic subjects did not show significant increased incidence of AMI during 6:01–12:00 hours (28.8%) rather there was increased incidence of AMI during 0–6:00 hours in 40 (66.7%). There was no significant difference with respect to age and gender (*p*-value 0.77 and 0.237).

Table-1: Demographics of the study population (Non-diabetics versus diabetics)

	Non-diabetic	Diabetic	*p*-value
Age	59.08±13.81	59.25±13.78	0.77
Male	69 (53.5%)	60 (46.5%)	0.237
Female	31 (43.7%)	40 (56.3%)	

Table-2: Comparison of circadian rhythm in groups

	Circadian rhythm				*p*-value
	0–6	6:01–12	12:01–18	18:01–24	
Non-diabetic	20	42	25	13	0.001
	33.3%	71.2%	52.1%	39.4%	
Diabetic	40	17	23	20	
	66.7%	28.8%	47.9%	60.6%	
Total	60	59	48	33	
	100.0%	100.0%	100.0%	100.0%	

Table-3: Gender and circadian rhythm

Circadian Rhythm			Gender		Total
			Male	Female	
0:00 to 06:00	Group	Non-diabetic	14	6	20
		Diabetic	22	18	40
	Total		36	24	60
06:01 to 12:00	Group	Non-diabetic	30	12	42
		Diabetic	10	7	17
	Total		40	19	59
12:01 to 18:00	Group	Non-diabetic	16	9	25
		Diabetic	15	8	23
	Total		31	17	48
18:01 to 24:00	Group	Non-diabetic	9	4	13
		Diabetic	13	7	20
	Total		22	11	33

DISCUSSION

It is evident from the data that AMI onset depicts a characteristic distribution during 24 hours rather than being random in non-diabetics and diabetics <5 years duration. The onset of ischemic AMI occurs more frequently in the early morning.[10] Time of onset of symptoms in patients with AMI follows a circadian rhythm. Increased platelets aggregation and reduction in fibrinolytic activity, which both occur during the morning, result in thrombotic events in patients with AMI and Acute ischemic stroke. Changes in platelet aggregation correlate with changes in plasma catecholamine levels, which actually increase early morning.[11] Significant circadian variations in symptom onset has been shown by the patients with ST-elevation AMI.[12] The normal circadian variation of onset of AMI can be modified by Diabetes, smoking and reinfarction.[13] It was shown by a local study that the characteristic circadian variation in AMI onset is altered in subjects with long standing diabetes mainly due to autonomic dysfunction.[14]

Autonomic dysregulation in the diabetic patients may be explained by the diabetic subgroup in another study which showed a circadian variation in on the set of AMI with a dual mode pattern involving one morning and one night peak.[13]

In diabetic subjects, the mechanism of circadian rhythm in the onset of AMI is not clear. It has been observed that approximately 16–50% of subjects with long-standing type 1 and type 2 diabetes have diabetic neuropathy which may present as mononeuropathy, polyneuropathy or autonomic neuropathy. Normal circadian pattern of autonomic nervous system activity is lost in patients with diabetic neuropathy.[15] Cardiac autonomic neuropathies are common chronic complications of diabetes which result into high morbidity.[16] Significant impaired heart rate and blood pressure variability has been reported in subjects with diabetes and symptomatic autonomic neuropathy.[17,18] It was seen in one study, there were abnormal findings in more than two of six autonomic function tests in 34.3% type 2 diabetic and 25.3% type 1 diabetic subjects.[19] Another study showed that circadian variation in AMI symptom onset occurred in subjects with type 2 diabetes of less than 5 years, on the other hand no such circadian variation existed in subjects with type 1or type 2 diabetes ≥5 years.[20]

There may be therapeutic implications owing to the loss of circadian rhythm in the onset of acute MI. As it has been shown that cardiac medications have their effects mainly by diminishing the morning peak in AMI, the most effective timing of such medications may vary in diabetic patients from their non-diabetic counterparts.[21]

In this study of early survivors of AMI, a circadian variation on the onset of AMI symptom was observed in patients with no diabetes. However, a marked attenuation in early morning peak (6:01–12 hours) in the onset of AMI was noted in patients with diabetes for ≥5 years. On the other hand, diabetic subjects showed increased incidence of AMI during 0–6:00 hours. Our study also demonstrated that patients with diabetes ≥5 years duration, have no particular pattern like those of non-diabetics when it comes to the time of onset of AMI. Biological rhythms can influence the presentation of diseases and study of circadian patterns can definitely help in predictability and management of diseases. The limitation of the study was the small number of subjects studied. The scope of the study can be validated by increasing the number of subjects.

CONCLUSION

Incidence of AMI is significantly increased in the morning 6:01–12:00 hours in subjects without diabetes. However, diabetic subjects did not show significant increased incidence of AMI during this time rather there was increased incidence of AMI during 0–6:00 hours.

Acknowledgment: This study was supported by Punjab Institute of Cardiology (PIC), Emergency Department and Department of Endocrine and Metabolism Services Hospital Lahore. No potential conflicts of interest relevant to this article were reported.

AUTHORS' CONTRIBUTION

SK: Contribution: literature search, conceptualization of study design, data collection, write-up. NK: Contribution: data collection, data analysis. HK: Contribution: data collection. RA: Contribution: data interpretation. HMFR: Contribution: proof reading

REFERENCES

1. Gaziam JM. Global Burden of cardiovascular Disease. In: Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia: Saunders Elsevier; 2008;1–22.
2. Ohira T, Iso H. Cardiovascular disease epidemiology in Asia: an overview. Circ J 2013;77(7):1646–52.
3. Gupta R, Joshi P, Mohan V, Reddy KS, Yusuf S. Epidemiology and causation of coronary heart disease and stroke in India. Heart 2008;94(1):16–26.
4. Sari I, Davutoglu V, Erer B, Tekbas E, Ucer E, Ozer O, *et al*. Analysis of circadian variation of acute myocardial infarction: afternoon predominance in Turkish population. Int J Clin Pract 2009;63(1):82–6.
5. Takeda N, Maemura K. Circadian clock and cardiovascular disease. J Cardiol 2011;57(3):249–56.
6. Hjalmarson A, Gilpin EA, Nicod P, Dittrich H, Henning H, Engler R, Blacky AR, *et al*. Differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction. Circulation 1989;80(2):267–75.
7. Behar S, Halabi M, Reicher-Reiss H, Zion M, Kaplinsky E, Mandelzweig L, *et al*. Circadian variation and possible external triggers of onset of myocardial infarction. SPRINT Study Group. Am J Med 1993;94(4):395–400.
8. Zarisch S, Waxman S, Freeman RT, Mittleman M, Hegarty P, Nesto RW. Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischemia in diabetes mellitus. J Am Coll Cardiol 1994;24(4):956 –62.
9. Rana JS, Mukamal KJ, Morgan JP, Muller JE, Mittleman MA. Circadian Variation in the Onset of Myocardial Infarction Effect of Duration of Diabetes. Diabetes 2003;52(6):1464–8.
10. Reiter R, Swingen C, Moore L, Henry TD, Traverse JH. Circadian Dependence of Infarct Size and Left Ventricular Function after ST Elevation Myocardial Infarction. Circ Res 2012;110(1):105–10.
11. Kumar S, Meraj L, Akhter I, Sultana I, Mufti MA, Junaid K. Circadian variation in the onset of Acute ischemic stroke. J Rawal Med Coll 2014;18(2):190–2.
12. Holmes DR Jr, Aguirre FV, Aplin R, Lennon RJ, Nestler DM, Bell MR, *et al*. Circadian Rhythms in Patients With ST-Elevation Myocardial Infarction. Circ Cardiovasc Qual Outcomes 2010;3(4):382–9.
13. Lopez Messa JB, Garmendia Leiza JR, Aguilar García MD, Andrés de Llano JM, Alberola López C, Ardura Fernández J. Cardiovascular risk factors in the circadian rhythm of acute myocardial infarction. Rev Esp Cardiol 2004;57(9):850–8.
14. Mishra P, Sahoo B, Bhimani N, Rathi N. Circadian variation in onset of myocardial infarction: Comparison between diabetics (Niddm) and non-diabetics. Natl J Integr Res Med 2013;4(6):107–10.
15. Li J, Hua Q, Pi L, Tan J, Li B. Circadian variation on the onset of acute ST segment elevation myocardial infarction in diabetic subjects. J Cardiovasc Dis Res 2010;1(1):23–6.
16. Pop-Busui R. Cardiac Autonomic Neuropathy in Diabetes: a clinical perspective. Diabetes Care 2010;33(2):434–41.
17. Poulsen PL, Ebbehoj E, Arildsen H, Knudsen ST, Hansen KW, Molgaard H, *et al*. Increased QTc dispersion is related to blunted circadian blood pressure variation in normoal buminuric type 1 diabetic patients. Diabetes 2001;50(4):837–42.
18. Yamamoto M, Yamasaki Y, Kodama M, Matsuhisa M, Kishimoto M, Ozaki H, *et al*. Impaired diurnal cardiac autonomic function in subjects with type2 diabetes. Diabetes Care 1999;22(12):2072–77.
19. Ziegler D, Gries FA, Spuler M, Lessmann F. The epidemiology of diabetic neuropathy. Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. J Diabetes Complications 1992;6(1):49–57.
20. Rana JS, Mukamal KJ, Morgan JP, Muller JE, Mittleman MA. Circadian Variation in the Onset of Myocardial Infarction: effect of duration of diabetes. Diabetes 2003;52(6):1464–68.
21. Fava S, Azzopardi J, Muscat HA, Fenech FF. Absence of circadian variation in the onset of acute myocardial infarction in diabetic subjects. Heart 1995;74(4):370–72.

Received: 19 July, 2017	*Revised: 18 September, 2016*	*Accepted: 17 May, 2017*

Address for Correspondence:
Suresh Kumar, Endocrinology Department services Hospital, Lahore-Pakistan
Cell: +92 334 241 6871
Email: sk_khurana1979@yahoo.com