Journal of Cardiovascular and Thoracic Research, 2012, 4(4), 113-117
doi: 10.5681/jcvtr.2012.027
http://jcvtr.tbzmed.ac.ir

Association between Diabetic Retinopathy and Left Ventricular Dysfunction in Diabetic Patients with Unstable Angina

Ebadollah Heidari[1], Sanaz Nematzadeh Pakdel[2], Jahanbakhsh Samadikhah[2], Rasoul Azarfarin[2], Kamran Shadvar[2*]

[1]*Department of Ophthalmology, Nikookari Hospital, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 10 July 2012
Accepted: 12 Oct 2012
ePublished: 30 Oct 2012

Keywords:
Unstable Angina
Diabetic Retinopathy
Left Ventricular Ejection Fraction

ABSTRACT

Introduction: Diabetes mellitus (DM) is associated with serious complications including macro- and microvascular problems such as diabetic retinopathy. Coronary involvement in diabetic patients is believed to be a consequence of microvascular complications. However, the available data are inconclusive and scarce. This study aimed to evaluate the probable association between diabetic retinopathy and left ventricular dysfunction in diabetic patients with unstable angina (UA). **Methods**: In this cross-sectional study, 200 diabetic patients with UA (100 cases with diabetic retinopathy and 100 cases without diabetic retinopathy) were enrolled in a teaching hospital. Left ventricular ejection fraction (LVEF) as well as the frequency of cases with left ventricular dysfunction (LVEF<50%) were compared between the two groups and different degrees of diabetic retinopathy (proliferative and non-proliferative). **Results**: Patients' demographic variables were comparable between the two groups. Mean diagnosis time of DM was significantly higher in the patients with diabetic retinopathy (8.40±6.60 vs. 3.81±3.58 years; P<0.001). Mean LVEF was significantly lower in the retinopathy group (50.50±6.91% vs. 53.07±4.87%; P=0.003). Frequency of cases with left ventricular dysfunction was significantly higher in the group with diabetic retinopathy (31% vs. 12%; P=0.001, OR=3.33, 95%CI: 1.58-7.14). The frequency of cases with left ventricular dysfunction was significantly yet independently higher in patients with proliferative vs. non-proliferative diabetic retinopathy. **Conclusion**: Left ventricular dysfunction is more common in diabetic patients with unstable angina and diabetic retinopathy compared with their counterparts without diabetic retinopathy.

Introduction

Diabetic retinopathy is one of the four leading causes of blindness in 20 to 74 year-old adults and a major cause of blindness all over the world. Prevalence of diabetesis up to 7% of the general population. It is estimated that 25% of the diabetic population has one form of diabetic retinopathy while 5% of the population suffers severe degrees of the disease. The prevalence of all types of diabetic retinopathy increases in the population parallel to the disease duration and onset age.[1-4] On the other hand, heart disease in diabetic retinopathy has shown to occur due to microvascular dysfunction. However, no simple and noninvasive evaluation of coronary microcirculation has been introduced and the existing studies suffer from technical flaws.[5-8]

Two decades ago, Framingham suggested that retinopathy symptoms may reflect a process of microangiopathy affecting the myocardium.[9] This hypothesis was confirmed by subsequent studies. In these studies, retinopathy signs with T-wave changes in ECG, coronary artery stenosis in the angiographic and histologic evidence of myocardial microvascular disease were associated.

Recent studies using photographic retinopathy grading have introduced stronger evidence on the relationship between this situation and cardiac dysfunction.[10,11] It has been recognized that diabetic retinopathy increases the risk of myocardial infarction, coronary artery disease and heart failure.[12-17] Due to the limitations and the importance of the previously performed studies, we decided to study the relationship between diabetic retinopathy and its severity in patients with unstable angina with left ventricular dysfunction.

Materials and methods

In this cross-sectional study after approval of the ethics committee of Tabriz University of Medical Sciences

***Corresponding author:** Kamran Shadvar , E-mail: k_shadvar@yahoo.com

and obtaining informed consent from all patients, 200 consecutive patients with unstable angina referred to Madani Heart Hospital were enrolled to investigate the presence of diabetic retinopathy and its relation with left ventricular dysfunction. Inclusion criteria were: 1) Type 2 diabetes mellitus patients with unstable angina; 2) Age of 40 years and older and 3) Willingness to participate in the study.

Exclusion criteria were: 1) Patients with a history of valvular heart disease; 2) A history of myocardial infarction; 3) Patients with cardiomyopathy and congenital heart disease; 4) Patients with chronic heart arrhythmias and 5) Patients with bundle branch block in ECG.

Patients were divided into two groups: 100 patients with retinopathy (case group) and 100 patients without retinopathy (control group). Case group, based on the grading & severity of retinopathy, was divided into four subgroups: Non-proliferative with mild, moderate and severe retinopathy and proliferative groups.

Retinopathy detection was made by an ophthalmologist and retina specialist who were unaware of the status of left ventricular function. Left ventricular function was assessed by a cardiology resident under attending supervision. It should be noted that these two individuals were also unaware of the patient's retinopathy status. In this study, left ventricular dysfunction was defined as LVEF<50%.

Age, sex, weight, height, body mass index (BMI), duration of diabetes mellitus, history of hypertension, history of alcohol consumption, dyslipidemia, left ventricular ejection fraction, ventricular dysfunction and smoking, family history of heart disease and type and severity of diabetic retinopathy were studied.

The obtained information is presented as the mean ± SD, frequency and percentage. SPSS statistical program version 15 was used. Quantitative variables were compared using Student T-test (Independent Samples). Qualitative variables (Categorical) were compared by Contingency tables using Chi-Squared test or Fisher's exact test. $P \leq 0.05$ was considered statistically significant.

Results

The average age (range) of patients in case group was 59.46 ± 9.06 (38-85) years and 59.08 ± 10.18 (42-79) years in the control group. There was no significant difference between two groups regarding patients'age (P= 0.79; Figure 1).In two groups, demographic characteristics, BMI, hypertension, dyslipidemia, smoking and family history of heart disease were not significantly different (Figure 2). The average duration of diabetes mellitus was significantly higher in case group (P<0.001; Figure 3). None of the patients had a history of alcohol consumption (Figure 4).

Mean LVEF in case group (50.50± 6.91%) was significantly lower than the control group (53.07 ±4.87%,P= 0.003; Figure 5).In case and control groups,31 and 12 patients had left ventricular dysfunction respectively. Percentage Of impaired left ventricular function was significantly higher in patients with retinopathy (P=0.001; Figure 6).

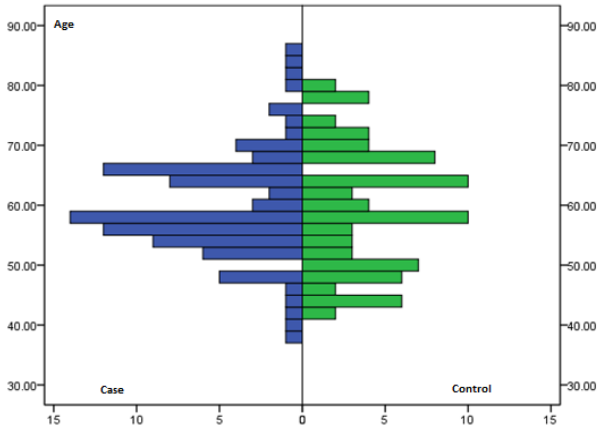

Figure 1. Age distribution of the patients with (case) and without (control) diabetic retinopathy

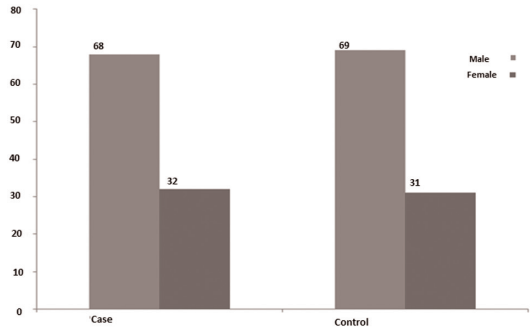

Figure 2. Gender percentage of the patients with (case) and without (control) diabetic retinopathy

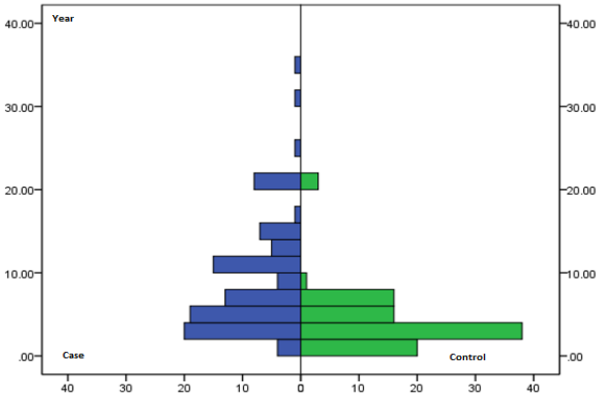

Figure 3. Duration of diabet in the patients with (case) and without (control) diabetic retinopathy

Study variables by type of diabetic retinopathy

Comparison between proliferative and non proliferative (Figure 7): Mean age, sex, and duration of diagnosed diabetes mellitus, hypertension and smoking history, and

family history of heart disease in the two groups were not statistically significant. Percentage of non-proliferative cases with a history of dyslipidemia group was significantly greater. The mean LVEF in proliferative group was significantly low. Percentage Of impaired left ventricular function was significantly greater in the proliferative group.

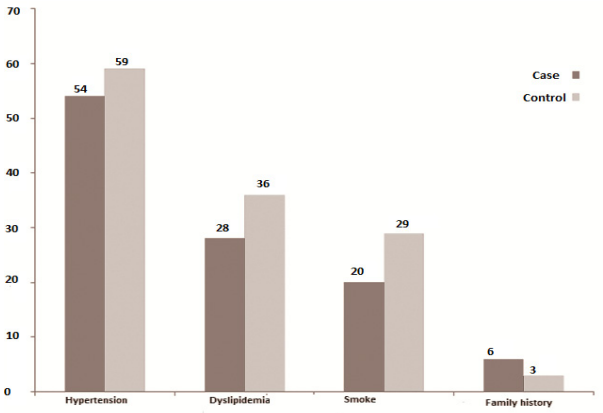

Figure 4. Risk factors percentage in the patients with (case) and without (control) diabetic retinopathy

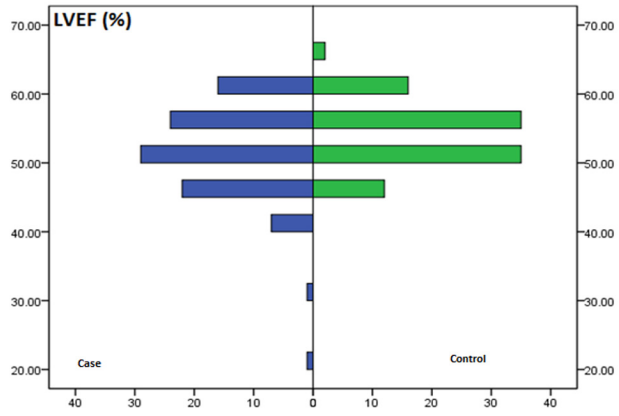

Figure 5. Left ventricular ejection fraction in the patients with (case) and without (control) diabetic retinopathy

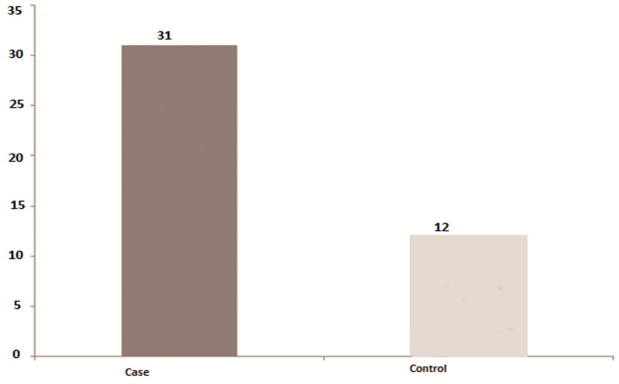

Figure 6. Left ventricular dysfunction in the patients with (case) and without (control) diabetic retinopathy

Comparison between Proliferative and non-Proliferative with different degrees of severity (Table 1): The average duration of diagnosed diabetes mellitus was significantly more in the proliferative group than the mild non-Proliferative groups. Percentage of cases with a history of hypertension was significantly higher in severe non-Proliferative group than other groups. Percentage of cases with a history of dyslipidemia in the proliferative group was significantly less than other groups. Comparing the frequency of cases with smoking history was not possible. The mean LVEF in the proliferative group was significantly less than severe non-proliferative groups. Percentage of impaired left ventricular function in 4 groups showed no significant difference. In other cases, there was no statistically significant difference.

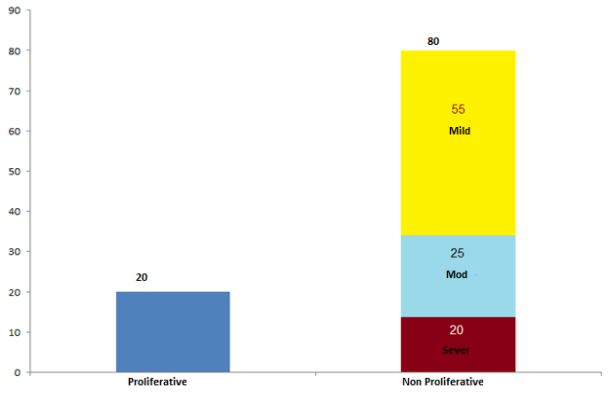

Figure 7. Type & severity of retinopathy in case group

Discussion

In this study, the relationship between diabetic retinopathy and left ventricular dysfunction in diabetic patients with unstable angina was evaluated. Accordingly, the mean LVEF in patients with diabetic retinopathy was significantly lower than the group without diabetic retinopathy. The percentage of impaired left ventricular function in patients with diabetic retinopathy was significantly higher.

It has previously been shown that the heart disease in people with diabetes mellitus as retinopathy is caused by microvascular dysfunction. In other words, the underlying pathophysiology in coronary artery disease and diabetic retinopathy is the same.[5-8]

Two decades ago, Framingham Heart Study suggested that retinopathy symptoms may reflect a microangiopathic process in which the myocardium is also involved.[9] This hypothesis was later approved by the future studies. In these studies, retinopathy signs were associated with T-wave changes in ECG, coronary artery stenosis in the angiographic and histologic evidence of myocardial microvascular disease.[10,11]

Recent studies using photographic retinopathy grading have introduced stronger evidence on the relationship between retinopathy and cardiac dysfunction. It has been

Table 1. Variables were compared according to the type and severity of diabetic retinopathy

	Non proliferative				Proliferative (n=20)	P*	P**
	Total (n=80)	Mild (n=44)	Mod (n=20)	Sever (n=16)			
Age (year)	60.4±9.29	59.9± 9.69	59.06± 8.97	61.71± 8.96	57.26± 7.94	0.23	0.55
Gender (male)	(67.5)54	(70.5)31	(75)15	(50)8	(70)14	0.83	0.39
BMI	27.94±6.09	27.21± 4.37	26.65± 2.33	31.16± 10.49	26.04± 4.43	0.27	0.08
Duration Of Diabet(year)	7.84± 5.97	6.16± 4.21	9.35± 7.15	10.73± 7.31	10.65± 8.46	0.08	0.01
Hypertension	(57.5)46	(45.5)20	(55)11	(93.8)15	(40)8	0.16	0.01
Hyperlipedemia	(33.8)27	(38.6)17	(25)5	(31.3)5	(5)1	0.01	0.04
Smoke	(16.3)13	(18.2)8	(15)3	(12.5)2	(35)7	0.11	-
Positive Family History CVD	(6.3)5	(4.5)2	(15)3	(0)0	(5)1	0.65	-
LVEF(%)	51.31± 5.99	50.23± 5.90	52.00± 6.77	53.44± 4.73	47.25±9.24	0.01	0.03
LV. Dysfunction	(26.3)21	(31.8)14	(25)5	(12.5)2	(50)10	0.04	0.09

Data are demonstrated as mean±SD or number (%), BMI: Body mass index, LVEF: Left ventricular ejection fraction, CVD: Cardio vascular diseases, LV: Left ventricle, *Proliferative vs. Non proliferative, **Proliferative vs. severities of Non proliferative

recognized that the diabetic retinopathy increases the risk of myocardial infarction, coronary artery disease and heart failure.

In a study, Frati *et al*. evaluated the diabetic patients without cardiovascular symptoms. This study demonstrated that left ventricular dysfunction has a significant relation with duration of diabetes and microvascular disease including diabetic retinopathy.[18] In Fuller and colleagues study, 1126 patients with type 1 diabetes and 3179 patients with type 2 diabetes were studied. After 12 years, diabetic retinopathy increased the risk of heart disease to 1.5 to 2 times in patients with type 2 diabetes. The increased risk was also observed in women with type 1 diabetes while in men with type 1 diabetes, the risk of heart disease was more than 2 times.[14]

Annonu *et al*. studied 66 type 1 diabetes patients without cardiovascular diseases. This study demonstrated that left ventricular dysfunction is associated with the duration of diabetes and diabetic retinopathy.[19] Klein and colleagues studied 996 patients with type 1 diabetes. Twenty years later, a significant relationship between severity of retinopathy and heart disease was reported.[16]

Wong and colleagues, in a similar study, studied 627 patients with type 2 diabetes. After 7 years, the risk of heart failure in people with retinopathy was more than 2 times than those without retinopathy.[13] Juutilainen and colleagues studied 824 patients with type 2 diabetes. After 18 years, proliferative retinopathy increased the risk of heart disease more than 2 times in these individuals compared to the controls. Only in women Non-proliferative retinopathy was reported as a risk factor for heart disease.[15]

Cheung and colleagues studied 1021 middle-aged patients with type2 diabetes with normal renal function and no symptoms of coronary artery disease and heart failure. Retinopathy severity and the incidence of heart failure and mortality associated with the severity of retinopathy were evaluated. Some (12.8%) of these patients had diabetic retinopathy. After 9 years, 10.1% of the patients developed heart failure. The incidence of heart failure in people with retinopathy was significantly higher (cumulative incidence of 6.12% vs. 5.8%). After controlling other risk factors, diabetic retinopathy increased the risk of heart failure by 2.5 times.[12]

Mishra and colleagues studied 73 diabetic patients without symptoms of heart disease. Echocardiographic systolic and diastolic function was assessed separately. Finally, it was shown that there was significantly higher number of diabetic retinopathy cases in patients with left ventricular dysfunction. Additionally, this status was significantly associated with duration of diabetes mellitus.[20] Aguilar and colleagues studied 531 patients with type 2 diabetes. In this study it was demonstrated that increase in these verity of retinopathy increased left ventricular mass and left atrial dimension and LVEF, independent of confounding variables, decreased.[17]

As can be seen, our results are in line with existing reports. In our study, significant association was present between diabetic retinopathy and duration of diabetes mellitus; left ventricular dysfunction independent of this parameter was significantly higher in the group with diabetic retinopathy. To the best of our knowledge, no similar study on patients with unstable angina has been conducted so far. In this study, the correlation between left ventricular dysfunction and the type and severity of diabetic retinopathy was studied. Accordingly, the percentage of impaired left ventricular function in patients with proliferative diabetic retinopathy was significantly higher than non-proliferative cases. However, after controlling for confounding factors, this significance disappeared.

Van Hecke *et al*. in their study on 2237 patients with type 1 diabetes mellitus showed that mortality from cardiovascular events in proliferative diabetic retinopathy is about 4 times higher than patients suffering from non-proliferative diabetic retinopathy. However, this relationship became insignificant after controlling for

other risk factors for cardiovascular disease.[21]

Reaven and colleagues showed that coronary calcium has a direct relationship with diabetic retinopathy. This relationship in patients with proliferative diabetic retinopathy was significantly higher than patients with non-proliferative diabetic retinopathy.[22]

As can be seen, the results of our study are in line with previous reports in this field. However, to evaluate more carefully, further studies with larger sample size are required.

Conclusion

In our study, 31% of diabetic patients with retinopathy and unstable angina had left ventricular dysfunction. While, in diabetic patients without retinopathy and with unstable angina, left ventricular dysfunction was seen in only 12% of cases. Percentage of impaired left ventricular function in patients with unstable angina and a sign of retinopathy are significantly higher than the group without retinopathy. There was no association between left ventricular dysfunction, type, and severity of diabetic retinopathy in patients with unstable angina. Although the risk of left ventricular dysfunction in patients with proliferative diabetic retinopathy is more than non-proliferative, in order to reach conclusive results, further studies with larger sample size are recommended.

Acknowledgment

This research project was funded by Cardiovascular Research Center, Tabriz University of Medical Sciences.

Conflict of interests: The authors declare no conflicts of interest.

References

1. Liesegang TJ, Skuta GL, Cantor LB. Retina & Vitreous. 25th ed. USA: LEO Publication; 2004.

2. Aiello LM, Cavallerano JD, Aiello LP, Bursell SE. Diabetic retinopathy. In: Guyer DR, Yannuzzi LA, Chang S, editors. Retina Vitreous Macula. 6th ed. USA: Saunders;1999.

3. Benson WE, Tasman W, Duane TD. Duane's Clinical Ophthalmology. 1st ed. New York: McGraw Hill;1994.

4. Crawford TN, Alfaro DV 3rd, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. **Curr Diabetes Rev** 2009;5:8-13.

5. Camici PG, Crea F. Coronary microvascular dysfunction. **N Engl J Med** 2007;356:830-40.

6. Duran JR 3rd, Taffet G. Coronary microvascular dysfunction. **N Engl J Med**. 2007;356:2324-5.

7. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. **J Am Coll Cardiol** 2003; 41:1387-93.

8. Pitkänen OP, Nuutila P, Raitakari OT, Ronnemaa T, Koskinen PJ, Iida H, et al. Coronary flow reserve is reduced in young men with IDDM. **Diabetes** 1998; 47:248-54.

9. Hiller R, Sperduto RD, Podgor MJ, Ferris 3rd FL, Wilson PW. Diabetic retinopathy and cardiovascular disease in type II diabetics. The Framingham Heart Study and the Framingham Eye Study. **Am J Epidemiol** 1988; 128: 402-9.

10. Breslin DJ, Gifford RW Jr, Fairbairn JF 2nd, Kearns TP. Prognostic importance of ophthalmoscopic findings in essential hypertension. **JAMA** 1966; 195: 335-8.

11. Duncan BB, Wong TY, Tyroler HA, Davis CE, Fuchs FD. Hypertensive retinopathy and incident coronary heart disease in high risk men. **Br J Ophthalmol** 2002; 86: 1002-6.

12. Cheung N, Wang JJ, Rogers SL, Brancati F, Klein R, Sharrett AR, et al. Diabetic retinopathy and risk of heart failure. **J Am Coll Cardiol** 2008; 51: 1573-8.

13. Wong TY, Barr EL, Tapp RJ, Harper CA, Taylor HR, Zimmet PZ, et al. Retinopathy in persons with impaired glucose metabolism: the Australian Diabetes Obesity and Lifestyle (AusDiab) study. **Am J Ophthalmol** 2005; 140: 1157-9.

14. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. **Diabetologia** 2001; 44: S54-64.

15. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. **Diabetes Care** 2007; 30: 292-9.

16. Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. **Diabetes Care** 1992; 15: 1875-91.

17. Aguilar D, Hallman DM, Piller LB, Klein BE, Klein R, Devereux RB, et al. Adverse association between diabetic retinopathy and cardiac structure and function. **Am Heart J** 2009; 1: 563-8.

18. Frati AC, Hurtado R, Ariza CR, Barjau R, Graef A, Rivera C, et al. Changes in ventricular function in diabetes mellitus. Relation to the duration of the diabetes and its complications. **Arch Inst Cardiol Mex** 1985; 55: 133-9.

19. Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. **J Am Soc Echocardiogr** 2001; 14: 885-91.

20. Mishra TK, Rath PK, Mohanty NK, Mishra SK. Left ventricular systolic and diastolic dysfunction and their relationship with microvascular complications in normotensive, asymptomatic patients with type 2 diabetes mellitus. **Indian Heart J** 2008; 60: 548-53.

21. van Hecke MV, Dekker JM, Stehouwer CD, Polak BC, Fuller JH, Sjolie AK, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. **Diabetes Care** 2005; 28: 1383-9.

22. Reaven PD, Emanuele N, Moritz T, Klein R, Davis M, Glander K, et al. Proliferative diabetic retinopathy in type 2 diabetes is related to coronary artery calcium in the Veterans Affairs Diabetes Trial (VADT). **Diabetes Care** 2008; 31:952-7.