ASSESSMENT OF CAD COMPLICATIONS IN DIABETIC AND NON DIABETIC POPULATION: A COMPARATIVE STUDY

Anjaneyulu C.S, Rao A.V and Prasad Venkata[a]*

[a]Medicine, NIMS, 12, Panjagutta, Hyderabad, Telanagana, 500012, India

Correspondence email: prasadvenkata@gmail.com

Abstract C*oronary Artery disease (CAD) is currently the leading cause of death worldwide and together with diabetes, poses a serious health threat, particularly in the Asian population. The risk factor management has evolved considerably with the continued emergence of new and thought-provoking processes. The laboratory investigations and population-based research findings and also unresolved controversies may pose dilemmas and conflicting impulses in most clinicians, and even more in well-informed patients. As results of the most recent clinical trials on glycaemic control for macrovascular risk reduction are woven into concrete clinical practice guideline. To understand the evidences of coronary artery disease complications with respect to diabetic and non diabetic is the need of the hour. Hence a study being carried out in a small pool of population of 120 subjects for understanding the clinical, biochemical, electrocardiography, associated risk factors complications and mortalities. It was observed that peaking of cardiac events were occurred in non diabetics and found to be significant. The central obesity was measured as a factor of waist to hip ratio and observed that gender won t play a vital role in both diabetic and non diabetics and it is statistically insignificant. Systolic dysfunction is common among diabetes on echocardiography. E-point septal Separation was higher among diabetics than non diabetics. Pump failure was an important cause of mortality and was commonly seen with females. Present findings in this study deliver a clear message for the risk management of complications associated with coronary artery disease in diabetic and non diabetic population.*

Keywords: Coronary Artery disease - diabetes - glycemic control - hypertension - lipid - risk factors.

INTRODUCTION

Diabetes mellitus (DM) is a common medical problem and a major risk factor for the development of atherosclerotic coronary artery disease (CAD). Worldwide, more than 100 million people have DM and this figure is projected to double in the next 20 years. In India alone, it is estimated that there are more than 20 million diabetics (1). There is no doubt that DM is going to be a major burden on the health care system in the 21st century. DM is not only associated with increased incidence and prevalence of CAD, but diabetic patients also have a 2-fold increase in mortality after acute myocardial infarction. This is an absolute medical emergency. It is suggested that type 2 diabetes is the one of the top five causes for mortality and affecting more than 170 million individuals worldwide (2). Premature cardiovascular morbidity and mortality is reported to be more common in diabetic subjects (3). The prevalence of diabetes and impaired Glucose tolerance are expected to be increased by 6.3% and 9% by 2025. The increase in the incidence of diabetes is more in developing countries i.e., 228 millions compared to that of developed countries i.e., 72million by 2030(4). It is going to manifest as epidemic of diabetes and CAD in developing countries especially in India. It is being observed as a mammoth burden on Indian economy. The SHARE study demonstrated that south East Asian had higher prevalence of cardiovascular disease compared to that of Europeans and Chinese living in Canada (5).

In India approximately 2.78 million deaths are due to cardiovascular disease of which over 50% is due to CAD (6). The CUPS (Chennai Urban Population Study) and CURES (Chennai Urban Rural Epidemiology Study) conducted on a representative population (aged>- 20 years). In CUPS survey demonstrated 11% of the total population had CAD and the age standardized prevalence was only 9.0% (7). About 1.2% had been documented with myocardial infarction and 1.3% had Q wave changes, 1.5% with ST segment and 7.0% T wave abnormalities.

The national urban diabetes survey (NUDS) (8) a landmark of epidemiological study showed that T2DM began at an earlier age in India and the prevalence of the disease was increased uniformly in all urban cities but concentrated in southern states of India. The major risk factors are racial predisposition, genetic risk, Age obesity, Insulin resistance and life style

changes due to the urbanization. The cardiac involvement in diabetes commonly manifests as CAD and less commonly as dilated cardiomyopathy and autoimmune cardiovascular neuropathy. The Framingham heart study assessed that the patients with diabetes that to woman exhibited an increased risk in coronary events including angina, stoke, heart failure, myocardial infarction.

Neither systolic blood pressure nor diastolic blood pressure was superior to the pulse pressure in predicting the CHD risk (9). It was observed that the prevalence of CAD in indian population is higher when compared to any other populations of the globe. The incidence of the CAD has increased from 6.5% to 12%. As per the CADI (Coronery Artery Disease in Asian Indian) the Indian patients with ACS have a higher rate of STEMI (61%) than do with developed countries (10). The latest risk factors for CAD among diabetics with microalbuminaria, PAI-I and hyper pro insulinaemia have appeared which have to be kept in mind while treating CAD because PAI-I may pose resistance to thrombolyis (Table-1). T2DM is the disease which has given rise to numerous complications. The major one being CAD clinical manifestations was found to be leading cause for diabetes death (Table-2). The present study was designed by keeping all these vital parameters such as spectrum of clinical presentation, risk aggregation, complications, and mortality in diabetic and non diabetic populations.

The main heading and paragraph styles can be applied using Word's style gallery. The heading styles automatically apply section numbering.

Table 1 Cardiovascular Risk Factors in Diabetes Mellitus.

Risk Factors	IDDM	NIDDM
Hypertension	+	++
Cigarette Smoking	-	-(may be additive)
Dyslipidemia		
Hyper TG	++	++
Low HDL	+/-	++
Small, Dense LDL	+	++
Increased apo B	+	++
VLDL	++	++
Family history of Atheroscleriosis	-	+
Obesity (central)	-	+
Hyperglycaemia	-	+

New Risk Factors for occurrence of CHD
1. Increased Plasminogen activator inhibitor (PAI-1) 2. Elevated levels of pro- insulin like molecules 3. Microalbuminuria 4. C-reactive protein

Table 2 Clinical Manifestation in Different Types of CAD.

Clinical Problem	Pathology	Clinical Features
Stable Angina	Ischemia due to fixed atheromatous stenosis of one or more coronary arteries	Central Chest Pain, Discomfort or breathlessness that is precipitated by exertion or other forms of stress
Unstable Angina	Ischemia caused by dynamic obstruction of coronary artery due to plaque rupture with superimposed thrombosis & spasm	Worsening angina (crescendo angina),angina on minimal exertion or angina or rest
MI	Myocardial necrosis cause by acute occlusion of a coronary artery due to plaque rupture & thrombosis	Chest pain, is cardinal symptom but breathlessness, vomiting, Anxiety, Collapse, Syncope.

MATERIAL AND METHODS:

The present study was designed as an observational study and it was undertaken at St.Theresa s Hospital, Hyderabad. The duration of the study was kept to 2 years. A total of 120 cases of CAD were studied out of which 60 subjects were prone to diabetic CAD and remaining 60 cases are non diabetic CAD. The samples were drawn by simple randomization technique. The diabetic CAD was termed as group 1 and non diabetic CAD as group 2.

Inclusion Criteria:

Group 1 (Diabetic CAD) Previously known diabetic or first time detected diabetic by American Diabetic Association.

Group-2 (Non Diabetic CAD)

The case presenting with myocardial infarction that are not known diabetic or not fulfilling ADA criteria.

Case presenting with CAD and with reactive hyperglycemia with glycol-Hb-6.3% of blood sugar coming to normal in the absence or insulin or OHA on follow up.

Exclusion Criteria:

Patients having impaired fasting glucose, impaired glucose tolerance [FPG

<126mg/dl. But >110mg/dl, PPPG 140-200mg/dl] presenting with CAD.

Diabetic CAD and non diabetic CAD subjects were recruited in the study as the inclusion and exclusion criteria. The clinical examination parameters such as stigmata of hypercholesterolemia and vital signs such as Pulse and BP were measured. The cardiac statuses were evaluated as per killip-kimball classification and finally ECG was also evaluated. The anthropometry parameters such as BMI and waist to hip ratio were also studied. The routine investigations such as CBP, CUE, FBS, RBS, Glycosylated hb, Lipid Profile and cardiac enzymes were studied.

STATISTICAL ANALYSIS:

All the values are expressed as mean+/- SD. The demographic characteristics of patient with or without diabetes and other unpaired variables are compared using unpaired student t-test. Categorical variable are measured with Yates correction of chi-square tests corresponding P values were calculated $P<0.05$.

RESULTS AND DISCUSSION:

The study was demonstrated in 120 patients divided into two groups of 60 members in one group. The study population included both the genders i.e., Group-1 a diabetic CAD consisting of 60 cases (42 males and 18 females) and Group-2 a non diabetic group with 60 cases (38 males and 22 females). The age and gender wise distribution of the diabetic and non diabetic cases with CAD are tabulated in Table 3. The age difference between two groups and within the groups and gender wise t-test shows insignificant $p>0.05$. Females were more commonly affected in the diabetic group than non diabetic group ($p<0.01$). We observed only pre-menopausal women had CAD among diabetic group whereas none were in pre-menopausal group among non diabetics.

The majority of the patients in diabetic group were presented with chest pain with sweating and with symptoms of sympathetic stimulation (vomiting 83.33%). A mere proportion of diabetic patients presented with breathlessness (20%),syncope(3.33%) and palpitation (8.33%).The onset of symptoms were divided into four quarters for assessing the diurnal variation of cardiac events (Table 4).

It is evident that among diabetic group events occurred uniformly throughout the day without any diurnal variation. Whereas the same in non diabetic the peaking of the events occurred in late morning that to in the second quarter following the circadian rhythm of cardiac events. The

distributions of the CAD according to their types were clearly depicted in the Table 5.

Table 3 Demographic representation and distribution of the cases on the basis of Age and Gender.

Age Group (Years)	Diabetic			Non diabetic			Total
	Male	Female	Total	Male	Female	Total	
35-44	2	2	4	3	1	4	8
45-54	14	5	19	15	10	25	44
55-64	14	6	20	9	6	15	35
65-74	7	3	10	7	4	11	21
75 Above	5	2	7	4	1	5	12
Total	42	18	60	38	22	60	120
Mean±SD	56±8.7	55±10.2	55.7±9.5	56.6±9.7	54.2±9.1	55.6±9.32	-----
p value	NS	NS	NS	NS	NS	NS	-----

Table 4 Diurnal Variations of the cardiac events observed in all the four quarters

Quarter	Diabetic		Non diabetic	
	No.	Percent	No.	Percent
First	12	20.00	5	8.30
Second	20	33.33	34	56.66
Third	17	28.33	14	23.33
Fourth	11	18.34	7	11.71
Total	60	100.00	60	100.00

X^2 =7.89 p<0.05 significant

Table 5 The Distribution of the type of CAD associated with diabetic and non diabetic cases.

CAD	Diabetic		Non diabetic	
	No.	Percent	No.	Percent
Stable Angina	33	55.00	40	66.66
Unstable Angina	17	28.34	12	20.00
Myocardial Infraction	10	16.66	8	13.34
Total	*60*	*100.00*	*60*	*100.00*

X^2=37.5 p<0.001 Highly Significant.

We observed that maximum number of cases of stable angina belonged to non diabetic group (66.66%) and unstable angina and MI belonged to diabetic group (28.34% 16.66%) respectively. There was a significant association between types of CAD among the diabetic and non diabetic groups (p<0.001). The duration of the diabetics among the patients were established and found that association between males and females with respect to duration was insignificant (p>0.05).The majority of the patients were on oral hypoglycemic agents (58%) and 27% of the patients were on insulin or combination with insulin and OHA.

In the study population 61.11% of females and 35.73% of males were hypertensive by history among the diabetics. On other hand in non diabetics 18.42% of males and 31.81% of females were of hypertensive. The treatments for the hypertension among the diabetic and non diabetic were mainly focused on calcium channel blockers respectively (34.62 % and 40%). The constitutional symptoms in diabetic group were found to be 16.66% and 15% were of retinopathy. There is no significant association with respect to smoking or tobacco or both in diabetic and non diabetic cases. The BMI was categorized in both the genders among diabetic and non diabetic and was clearly tabulated in the table 6.

Table 6 Categorical assessment of the genders based on BMI among diabetic and non diabetic population.

Category	Diabetic (Males)	NonDiabetic (Males)	Diabetic (Females)	NonDiabetic (Females)
Ideal	17	24	5	11
Over weight	11	08	4	7
Obese	14	5	9	3
Under Nourished	00	01	0	01
Total	42	38	18	22

Among Diabetic and non diabetic $X^2=3.98$ $p>0.05$ *(insignificant)*
In diabetic among male and female $X^2=9.5$ $p<0.05$ *(Significant)*
In non diabetic among male and female $X^2=16.12$ $p<0.05$ *(Significant)*

It is clear from the data that diabetics are more obese than non diabetics. Non diabetics have ideal body weight 58.33% than diabetic 36.66% $p<0.001$ highly significant, where as proportion of overweight people was found to be same in both diabetic and non diabetic groups. A significant association was found with BMI among diabetic and non diabetic group with a statistical significance of $p<0.01$. The waists to Hip ratio were studied among males and females of both diabetic and non diabetic group. In diabetic group 90.48% of males and 88.88% of females and in non diabetic group 97.37% of males and 86.36% of females were studied. The waist to hip ratio study concluded that there is no significant association between diabetic and non diabetic groups. One the other hand it was found that 55% of patients were hypertensive and 18.33% were pre hypertensive and the remaining 26.66% had normal blood pressure among the screened diabetic patients.

In non diabetic 36.66% were hypertensive and 46.67% pre hypertensive and 16.67% are with normal blood pressure. The systolic and diastolic blood pressure of diabetic and non diabetic groups were significant respectively ($p<0.01$). Both the groups had higher systolic blood pressure ($p<0.01$) and higher diastolic blood pressure ($p<0.05$).

In the measurement of random blood sugar levels for both the groups it was observed that no significant association between the RBS of diabetic and non diabetic male and female groups respectively. It is evident from the data that there was no significant difference between FBS and RBS in males and females of both the groups. But the

males had higher PPBS as compared to that of females (p>0.1). The data is represented in the form of tabular form for easy integration (Table 7).

Table 7 Fasting, Post Pranadial and Random blood sugar estimation among males and females of the study population

GENDER	Fasting Blood Sugar	Post Pranadial Blood Sugar	Random Blood Sugar
Males	172.6±54.7	248.32±58.2	242.2±93.4
Females	175.6±47.7	237.92±46.2	240.2±90.2
P Value	>0.01 (NS)	>0.01 (NS)	>0.1 (NS)

Values are expressed in mg/dl±SD

It was found that there was no much difference in the glycaemic control among males and females in diabetic group. 21.7% had good control 26.66% had fair control and 51.4% had poor control of blood sugar levels. The diabetic and non diabetic groups examined with respect to lipid profile and found that the maximum number of cases belonged to low risk category with total cholesterol, triglycerides and LDL cholesterol but with border line risk of HDL cholesterol. It was found that there was significant association between microalbuminuria and diabetic retinopathy. The cardiac functions of the patients were assessed using ECG. Among the patients the systolic dysfunction is commonly found in diabetics rather than in non diabetics (41.66% vs. 26.67%) The diabetics are more vulnerable to the death i.e., mortality than non diabetics (p<0.05).In totality 18 cases were reported in diabetic group that corresponds to 30% mortality and 8 cases in non diabetic group with a mortality of 13.33%.The main cause of the death was due to the pump failure in diabetic group and in non diabetic group pump failure along with ventricular arrhythmia and was accounted to be 50 % and 75% respectively.

DISCUSSION:

Cardiovascular diseases including CAD are more common among diabetic rather than non diabetics. There are lots of controversies with respect to the clinical profile of CAD and the risk factors associated with CHD and mortality patterns are the need of the hour. In the present investigation we compared the clinical biochemical and electrocardiographic profile of 120 cases of with and without diabetes. The mean age group was 55.7± 9.5 years among diabetics and 55.6±9.32 of non diabetics. There was no much difference between the age patterns of two groups. During the study we saw cut off of cases with respect to age and sex. It was observed that males

are commonly affected in both the groups. It is known fact that females have protection against IHD before menopause but this protection was effectively erased in the presence of diabetes. As per rancho and bernado (11) study diabetic females are commonly involved and death is more common among them.

In our study we found that there was no significance difference between age in both the groups at a significant level of $p>0.05$. The age difference between and with the groups were also found to be insignificant. The authors singer DE et.al.,(12) and Malmberg et al.(13), noted the same results and proved that the diabetic were older which agrees with our study. There was no much difference in the involvement of younger age group of about <40 years. The maximum complications or events were occurred in the age group of 50-59 years in both diabetic and non diabetics. Considering the above scenario we can say that age is an important risk factor for CHD in both the study population.

In framingha 72 study with biennial ECG examination, among 5127 participants 708 MI have been accounted to be more than 25% of discovered ECG only. Half of them had a typical symptoms and half of them were of asymptomatic i.e., truly silent. According to soler et al., (14) 33% of diabetics had a typical features and present with heart failure, hyperglycemia, vomiting and intern leading to increased mortality. The cardiovascular events with respect to acute Q wave MI, pulmonary edema and sudden death or variation in onset, peak incidence in late morning may lead to mortality (15). But where as in diabetics such circadian rhythm in q-wave IHD was lost and the events occurred throughout the day in a uniform fashion. The reasons are not clear or it may be due to increase platelet aggregation and autoimmune dysfunction. In our study the uniform distribution of quarters in diabetic and non diabetic groups helped us to understand the peaking of the events. More prominent peaking of events were presenting the morning and found to be statistically significant $p<0.05$. Similar kinds of results were obtained from Tanaka, T et.al.,(16) , which emphasized on the absence of circadian rhythm in untreated diabetic CHD. Treatment with Beta blockers aspirin and other drugs re establishes such variations. However loss of circadian rhythm was not seen in diabetics in GUSTO and TIMI-II trials.

During the study 17% of the cases were newly detected and 83% were of the established diabetic ones. We have observed that 55% of the cases are of stable angina 28.34% unstable angina and

16.66% of were of diabetes of CAD but only 15% were presented with diabetic retinopathy. The observations have witnessed that macro vascular complications are independent on the duration where as micro vascular changes are depended on the extent of the disease. The study revealed that 26 cases of diabetics out of which 15 are males and 11 are females where as in non diabetic out of 15 cases 7 males and 7 females were hypertensive by history. When compared to GUSTO trial 35% of non diabetic and 54.5% of diabetic were hypertensive by history. The study correlates with us and it is statistically insignificant.

The diabetic and non diabetic smoker has no significant difference. Whereas the diabetic male and female has got significant association and also the non diabetic male and female are statistically significant at $p<0.001$. The results were in concurrence to that of GUSTO and Ranchio bernado study. The familial history of diabetics of 5% and 6% of non diabetic were noted in IHD. The same was also noticed in the GUSTO-1 trial. The results were statistically insignificant.

The systolic and diastolic blood pressure were screened and found that higher among diabetics ($p<0.01$) and diastolic was also higher ($p<0.05$). The results were similar to that of GUSTO-1 trial. According to the study conducted by verbiti et. al.,(17) increment in BP is more commonly seen in nephropathy sets in than when it is absent ($p<0.02$) such increment was seen in both systolic and diastolic blood pressure. In our study we could not study such changes because of small number of patients who literally developed nephropathy.

The mean BMI was higher in diabetics when compared to that of non diabetics 25.4±3.1 and 24.02±2.51 respectively. The association was found to be statistically significant ($p<0.001$). In both the groups the females were more obese than males. In GUSTO Trial the BMI was higher among the diabetics i.e., 26% vs 26%). In rancho Bernard study the BMI was high among diabetics; the males commonly had higher BMI than females unlike in our study. The similar kind of results was obtained in laasko and pyorala (18) in finland, BMI was higher in women which was correlated with our study.

The central Obesity in our study presented 90.8% of males and 88.8% of females in diabetic group and 97.3% of males and 86.3% of females in non diabetic group. The association was insignificant between W: H among diabetic and non diabetics ($p>0.05$). In a separate study conducted by PM Mckeigu (19) the south Asian immigrants had higher W:H ratio which

correlated to increased blood pressure and higher Triglycerides levels as compared to British population.

The total cholesterol levels in diabetic and non diabetic were found to be 13.3% is of high risk range. The TG levels in both the groups were evaluated and found that diabetics had higher TG levels when compare to non diabetics and the association was found to be $p<0.05$. In other words the diabetics had higher TG, low HDl and Low LDL as compare to non diabetics. The female LDL levels are higher in diabetic group and in non diabetic the males have got more TG levels compared to other gender. Lehto et.al.,(20) observed that the diabetics who had CHD events and the mortalities had higher TG and low level of HDL and low HDL/TG ratio. Rancho bernando study has also published similar kind of results and emphasized that the dyslipidemia is common phenomenon in woman and hence the mortality. The ECG study revealed 41.66% of diabetics had systolic dysfunction when compared to 26.66% of non diabetics.

On an average25 % of diabetics and 33.33% of non diabetic s isolated systolic dysfunction is commonly noted among diabetics. Shapiro et.al.,(21) and Uusitupa et.al.,(22) have noted the presence of diastolic dysfunction in the absence of hypertension and postulated it is because of cardio myopathy. Such dysfunction correlates with micro vascular complications which are especially seen with retinopathy. These studies have excluded the IHD hence we could not compare it with our study. The death rate or mortality among the diabetics (30%) and 13.33% among non diabetics revealed that pump failure is a common phenomenon which is leading to the death of especially males. The pre Thrombolytic and thrombolytic era proved that the pump failure is an important cause of mortality among women in the study. The no diabetics thus underline the EF as a important factor in diabetic cardiomyopathy which reduces the myocardial reserve.

CONCLUSION:

Diabetics had considerably higher percent of typical and atypical presentations. Hence CAD should be considered as one of the vital parameter in differential diagnosis of diabetics who have presented with chest pain. However the less severe it may be. Diabetics have a higher risk of factor profile and poor clinical outcome and hence they should be observed keenly for complications and especially to be looked for pump failure. Treating such complications vigorously will reduce the mortality among the diabetics with CAD.

It is recommended that good glycaemic control and maintenance of normal blood pressure reduces the bad cholesterol level. It is mandatory to monitor and regular follow-up of cholesterol will avoid CAD related morbidity and mortality. Good education and awareness among life style modification, quitting of smoking are important tools to overcome CAD and which will lead to a happy and healthy life.

REFERENCES:

1. World Health Organization. World Health Statistics. *Department of Measurement & Health Information Systems of the Information, Evidence and Research Cluster.* Geneva: WHO Press; 2008. p. 29-31.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53.
3. Swerdlow AJ, Jones ME. Mortality during 25 years of follow-up of a cohort with diabetes. Int J Epidemiol. 1996 Dec;25(6):1250-61.
4. M. M. S. Ahuja, B. B. Tripathy, Sam G. P. Moses, H. B. Chandalia, A. K. Das, P. V. Rao and S. V. Madhu (eds). RSSDI Textbook of Diabetes Mellitus 2nd edition Edpidemology of DM in developing countries,the scenario in Asia pp171 2002.
5. Health Situation in the south East Asia region 1998-2000. World Health Organization, Regional Office for south East Asia: New Delhi, India, 2002.
6. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, Kelemen L, Yi C, Lonn E, Gerstein H, Hegele RA, McQueen M. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE) Lancet. 2000 Jul 22;356(9226):279-84.
7. Hurst RT, Lee RW (2003) Increased incidence of coronary atherosclerosis in type 2 diabetes mellitus: Mechanisms and management. Ann Intern Med 139(10): 824 34.
8. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, Rao PV, Yajnik CS, Prasanna Kumar KM, Nair JD; Diabetes Epidemiology Study Group in India (DESI).High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia. 2001 Sep;44(9):1094-101.

9. Stanley S. Franklin, Shehzad A. Khan, Nathan D. Wong, Martin G. Larson and Daniel Levy Framingham Heart Study: Is Pulse Pressure Useful in Predicting Risk for Coronary Heart Disease?:Circulation 1999;100:354-360.

10. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, Gupta R, Joshi P, Kerkar P, Thanikachalam S, Haridas KK, Jaison TM, Naik S, Maity AK, Yusuf S; Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet. 2008 Apr 26;371(9622):1435-42

11. Barrett-Connor E: The Rancho Bernardo Study: 40 years studying why women have less heart disease than men and how diabetes modifies women's usual cardiac protection. Glob Heart. 2013 Jun 1;8(2).

12. Singer DE, Moulton AW, Nathan DM. Diabetic myocardial infarction. Interaction of diabetes with other preinfarction risk factors. Diabetes. 1989 Mar;38(3):350-7.

13. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000 Aug 29;102(9):1014-9.

14. Soler NG, Bennett M, Lamb P, Pentecost BL, Fitzgerald MG, Malins JM: Coronary care for myocardial infarction in diabetes. Lancet 1, 475 ,1974.

15. Nathan DM, Meigs J, Singer DE. The epidemiology of cardiovascular disease in type 2 diabetes mellitus: how sweet it is ... or is it? Lancet. 1997 Jul;350 Suppl 1:SI4-9.

16. Tanaka T, Fujita M, Fudo T, Tamaki S, Nohara R, Sasayama S. Modification of the circadian variation of symptom onset of acute myocardial infarction in diabetes mellitus. Coron Artery Dis. 1995 Mar;6(3):241-4.

17. Viberti GC, Messent J. Risk factors for renal and cardiovascular disease in diabetic patients. Cardiology . 1991;79:55 61.

18. Laakso M, Lehto S, Penttilä I, Pyörälä K. Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin-dependent diabetes. Circulation. 1993 Oct;88 (4 Pt 1):1421-30.

19. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet. 1991 Feb 16;337(8738):382-6.

20. Lehto S, Ronnemaa T, Haffher SM, Pyorala K, Kallio V, Laakso M. Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. Diabetes 46: 1354 359, 1997.

21. Shapiro B, Nishimura R, McGoon M, et al. Diagnostic dilemmas:diastolic heart failure causing pulmonary hypertension, pulmonaryhypertension causing diastolic dysfunction. Adv Pulmon Hypertens. 2006;5:13 20.

22. Uusitupa M, Mustonen J, Laakso M, *et al.* Impairment of diastolic function in middle aged type 1 and type 2 diabetic patients free of cardiovascular disease. Diabetologia, 1988, 31, 783-91.