The link between type 2 diabetes mellitus and reduction of ejection fraction

Akef Khoiled[1] , Marwa Abdeltawab[2]

Mohamed Mansour[3], Dina Abdelfatah[4],Khalid Refaat[5].

[1,3]*Physiology Departement ,Faculty of Medicine, Cairo University ,Egypt.*

[2]*Physiology Departement , Faculty of Medicine ,Benisuef University ,Egypt.*

[4]*Biochemistery Departement, Faculty of Medicine, Cairo University,Egypt.*

[5]*Cardiology Departement, Faculty of Medicine, Benisuef University ,Egypt.*

ABSTRACT

Type 2 diabetes mellitus has great relationship with heart failure In this study we try to clarify contribution of type 2 diabetes mellitus(T2DM)in inducing development of heart failure.50 people shared in this study which were divided into two groups, control group consisted of 20 subjects (15 males and 5 females) and diabetic group consisted of 30 patients(15 males ,15 females) who are admitted to cardiology department of Benisuef university hospital. EF is highly significant decrease in diabetic group with mean value50.84±7.86 % when compared to control group with mean value72.95±4.64 % (p-value <0.001). This study revealed that incidence of development of heart failure increases markedly in presence of T2DM.

Key words: *T2DM, heart failure, ejection fraction*.

1.Introduction:

Patients with diabetes have high incidence for development of heart failure . Diabetic patients with HF usually have cardiac risk factors including hypercholesteremia, obesity, and hypertension **[1]** and consequently patients with diabetes with a history of heart disease (e.g., coronary heart disease **(CHD)** are at a higher risk for developing cardiovascular events earlier in life than those without heart disease**[2]**. Chronic heart failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood**[3]**. Systolic heart failure causes impairment in the contractility of the heart and is determined when the left ventricular ejection fraction is less than 45%, while Diastolic dysfunction decrease the heart's ability to relax and fill with blood **[4]**. Diabetic cardiomyopathy can be defined as myocardial disease in patients with diabetes that cannot be related to any other known CVD, such as hypertension**[5]**. These changes in the structure and function of the heart in diabetic cardiomyopathy makes patients with diabetes are susceptible to heart failure with the early onset of the disease. The prevalence of asymptomatic diastolic dysfunction in patients with type 2 diabetes to be between 52 and 60%, despite meeting clinical criteria for acceptable glycemic control**[6] & [7]**. The aim of this study is to determined to how much extent is type 2 diabetes mellitus responsible to development of heart failure.

2.Materials and methods:

2.1.Criteria of the sharing subjects:

50 subjects participated in this study from March to June 2013 in which their ages ranged from 45 to 70 and their body mass index ranged from 30 to 35. They were divided into two groups, control group consisted of 20 individuals (15 males and 5 females) and diabetic group consisted of 30 individuals (15 males and 15 females).We took the agreement from each subjects for their participation in this study

.To choose subjects for diabetic group we took in consideration exclusion criteria which include type 1 diabetes mellitus from the history of the onset of the disease and also other causes of HF from the data found b echocardiography reports. Duration of development of diabetes ranges from six to ten years. They are admitted to hospital of benisuef university at department of cardiology. First we calculated BMI for each subject using the formula weight in kg / (height in meter)^2.

2.2.Collection of blood sample:

Fasting blood samples were collected by venipuncture in a test tube, samples allowed to clotted then centrifuged ,the clot was removed by centrifuging at 1,000-2,000 x g for 10 minutes in a refrigerated centrifuge, so the resulting supernatant is designated serum which was transferred into a clean polypropylene tube using a Pasteur pipette.

2.3.Measurment of glucose and lipid profiles:

Glucose was measured by glucose oxidase method using available commercially kit by **[8]**. Total cholesterol was measured by using The Cholesterol Enzymatic Assay Kit which is a plate-based colorimetric enzymatic assay for the determination of cholesterol in serum samples .The kit uses a spectrophotometric assay to detect cholesterol directly from serum samples. Concerning measurement of serum triglyceride, we used Serum Triglyceride Quantification Kit which depends on formation of lysis by a coupled enzymatic reaction system. First, lipase hydrolyzes the triglyceride ester bond, yielding glycerol, which is then phosphorylated and oxidized, producing hydrogen peroxide which reacts with the kit's Colorimetric Probe (absorbance maxima of 570 nm).HDL was measured by HDL Cholesterol Assay Kit supplied , this kit uses a spectrophotometric assay to detect HDL directly from serum samples due to presence of a specific reagent formulation to selectively stabilize non-HDLlipoprotein particles (LDL, VLDL and chylomicrons) while leaving HDL particles untouched. Next a second reagent containing a detergent and modified enzymes selectively reacts with the cholesterol present only in the HDL particles to form hydrogen peroxide. The hydrogen peroxide product then reacts with N-(2-hydroxy-3-sulfopropyl)-3,5-imethyoxyaniline to form a colored product. The resulting color change is measured at 610 nm and is proportional to the amount of HDL cholesterol originally present in the sample. We calculated LDL by using Friedewald equation: **LDL =total cholesterol-HDL-(TG/5).**

2.4. Measurment Ejection fraction:

Ejection fraction was measured by echocardiography with a 2.5MHz transducer. LV mass was estimated according to the American Society of Echocardiography recommendations based on the average of five measurements of LV diameters and wall thickness. When optimal orientations of M-mode recordings were impossible, linear dimension measurements were made using two-dimensional imaging**[9]**. LV volumes and ejection fraction were estimated using Simpson's modified biplane method based on three measurements. LV mass and volume measurements were corrected for body surface**[9]**. Endocardial border detection was enhanced by use of Coded second harmonic imaging **[10]**.

2.5.Statistical method:

Data were coded and entered using the statistical package SPSS version 21. Data was summarized using mean ±standard deviation. Comparisons between groups were done using unpaired T test**[11].**Correlation was done to test for linear relations between quantitative variables by Pearson correlation coefficient. P-values less than 0.05 were considered as statistically significant.

3.Results:

In our study we observed that high percentage of diabetic patients suffer from dyslipedimia and reduction in EF%. Table (1) showes that there are high significant increase of total cholesterol &TG and LDL level and high significant decrease of HDL in diabetic group with their mean values are 247.13± 51.45 mg/dl&157.68±34.98mg/dl&175.90±54.59mg/dl and 38.65±7.91mg/dl respectively in comparison to control group with their mean values are 141.95±27.77 mg/dl & 88.70±18.54 mg/dl &69.50±27.66 mg/dl and 54.85±8.72 mg/dl respectively (p-value <0.001).At the same time high significant decrease in EF% was noticed in diabetic patients with mean value 50.84±7.86 % when compared to control group with mean value72.95±4.64% (p-value <0.001).From another view table (2) & figures (1,2,3,4,5) reveale that EF% has negative correlation with glucose , TC, TG and LDL while has positive correlation with HDL.

Table(1):Comparison of EF%, glucose, total cholesterol , TG,LDL and HDL levels between diabetic and control groups:

	Control group (mean± SD)	Diabetic group (mean± SD)	p- value
Glucose gm/dl	85±8.00	289±43.87	<0.001*
TC mg/dl	141.95±27.77	247.13±51.45	< 0.001*
TG mg/dl	88.70±18.54	157.68±34.98	< 0.001*
LDL mg/dl	69.50±27.66	175.90±54.59	< 0.001*
HDL mg/dl	54.85±8.72	38.65±7.91	<0.001*
EF%	72.95±4.64	50.84±7.86	<0.001*

*p-value <0.001 indicates highly significant. Mean ±SD is highly significant increased in diabetic group than contol group.

Table (2): Correlation between EF% and other parameters:

	Glucose	TC	TG	LDL	HDL
Correlation with EF%	-.788**	-687**	-636**	-670**	.529**

**. Correlation is significant at the 0.01 level. EF% has -ve correlation with glucose, TC, TG and LDL but has +ve correlation with HDL

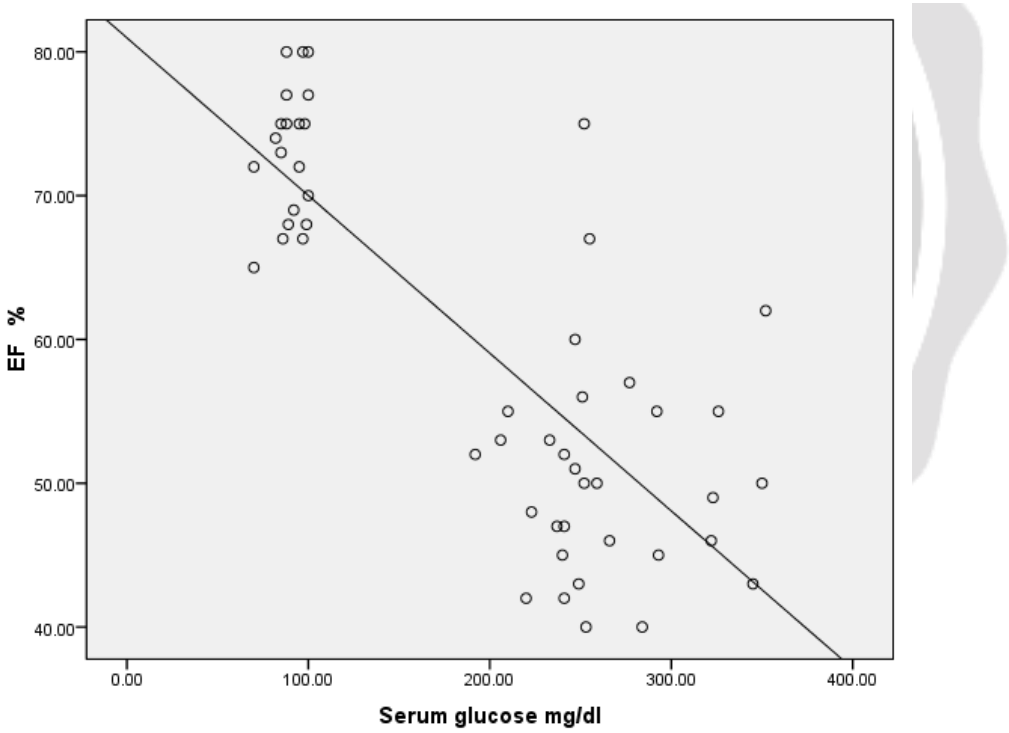

Figure (1): Negative correlation between EF% and glucose.

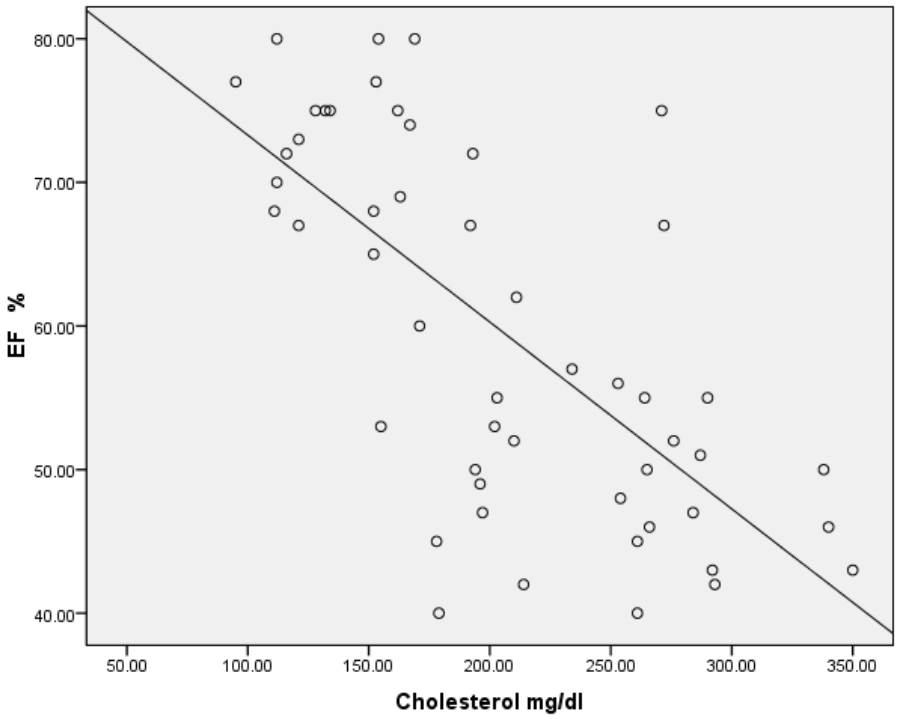

Figure (2): Negative correlation between EF% and total cholesterol.

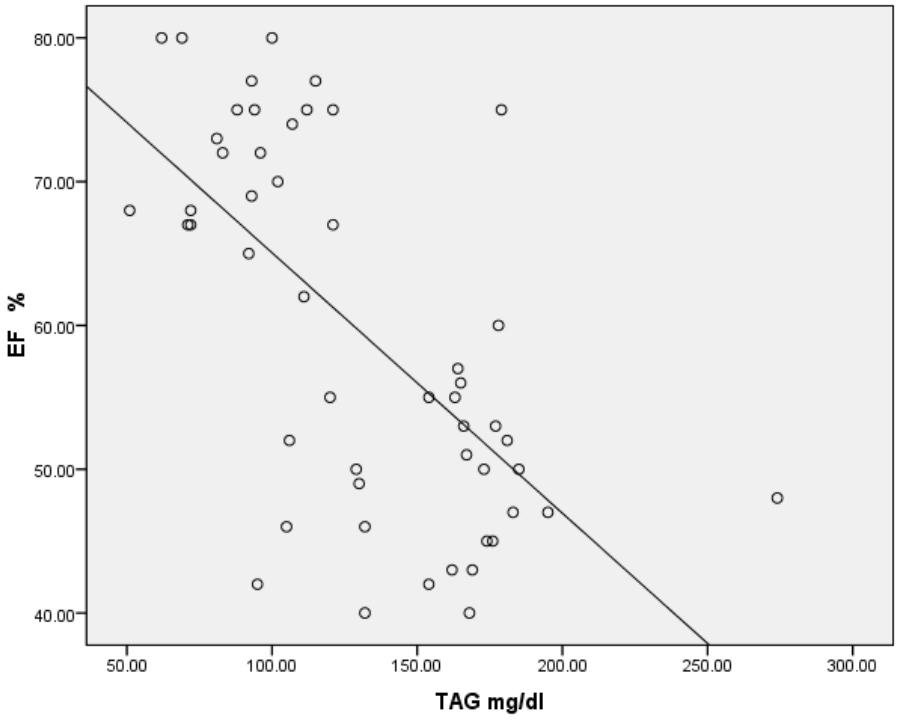

Figure (3): Negative correlation between EF% and TG.

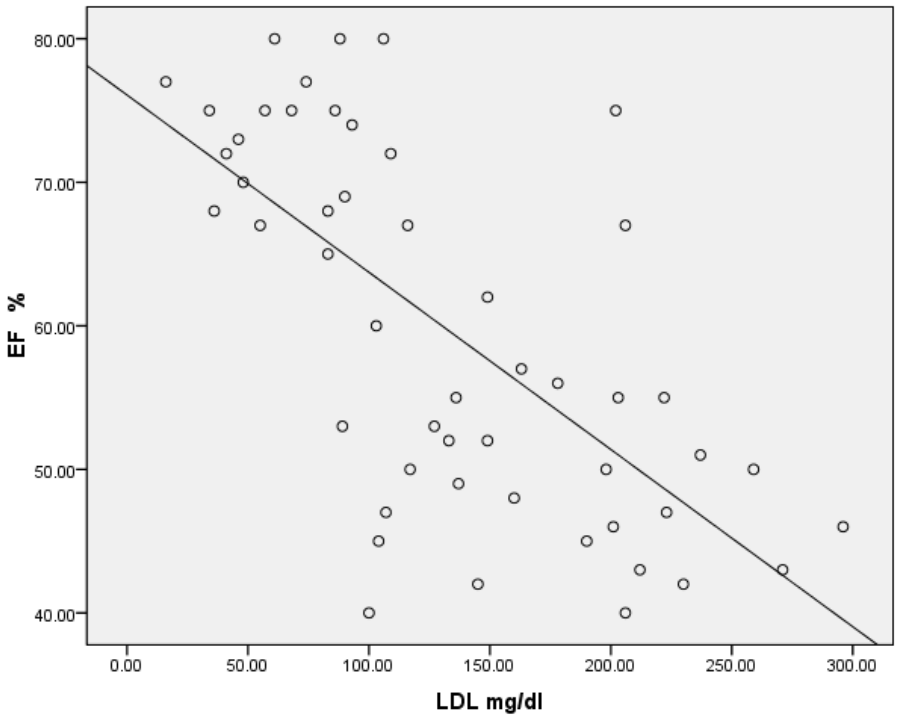

Figure (4): Negative correlation between EF% and LDL.

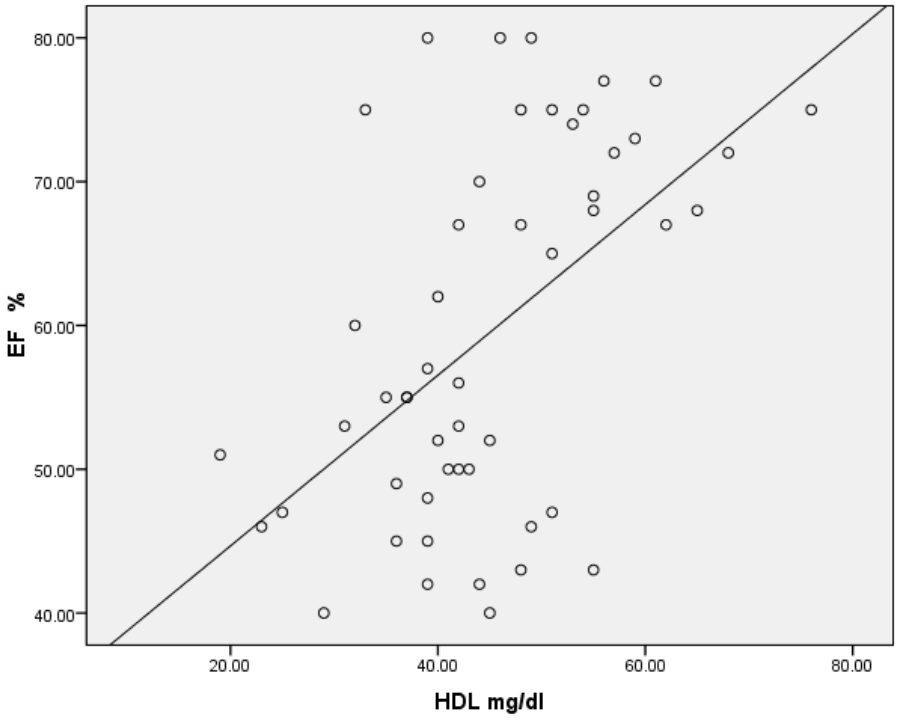

Figure (5): Positive correlation between EF% and HDL.

4.Discussion:

The most important result of our study is that diabetes is usually associated with reduction in left ventricular ejection fraction as reported by **[12].**while,**[13]** did not report a difference in EF between diabetic and non-diabetic patients despite some studies demonstrated a slightly lower LVEF in diabetic patients **[14]&[15].**Many theories tried to explain the mechanisms responsible for decreased myocardial contractility in the diabetic patients. Metabolic disturbances in diabetes are mainly developed by hyperglycemia **[16]** and consequently hyperglycemia considers an important factor that increases the risk for the development of heart failure in patients with diabetes. On the other hand ,as type 2 DM is a combination of, insulin resistance with hyperinsuliemia,hyperglyc--emia and increased nonesterified fatty acids, which contribute to lipotoxicity , oxidative stress, advanced glycation end products **(AGEs)**, and altered calcium handling and substrate metabolism**[17] & [18]** ,so these changes promote fibrosis, apoptosis, and myocyte hypertrophy in the myocardium, leading to structural and functional disturbance of the heart **[19]**. Pressure overload also produces changes in molecular signaling pathways which lead to similar harmful effect on structure and functional changes**[20**].Another mechanism includes that cardiac efficiency is decreased in diabetes because of increased fatty acid utilization, with increasing in ROS production **[21]** as the increase in oxidative stress in diabetic hearts results in decrease in NO levels, worsen endothelial function, and induce myocardial injury through stimulation of inflammatory mediators **[22]**. We found also in our study that total cholesterol ,TG and LDL are significantly increased while HDL level was significantly decreased in diabetic patients rather than control people.Both **[23]**& **[24]** found the same result.Triglycerides levels are increased in diabetes for many causes, primarily due to increase hormone-sensitive lipase **(HSL)** activity , this enzyme is concerning with release of stored triglycerides from adipocytes and conversion free faty acids and monoglycerides then transferred across the plasma membrane of the cell,this enzyme is normally inhibited by insulin**[25]**.One the other hand, the action of lipoprotein lipase **(LPL)** enzyme that concerning with breaking down of triglycerides is less effective in insulin-resistance, so the condition is associated also with diminished triglyceride clearance from the blood **[26]. [27]**reported that insulin deficiency reduces the activity of hepatic lipase plus several steps in the production of biologically active lipoprotein lipase. **Conclusion:** There are great relationship between presence of type 2 DM and development of heart failure **.** Diabetic patients have usually dyslypediemia with hypercholesterolemia**,** hypertriglyceridemia**,**high LDL and low HDL at the same time they suffer from reduction of EF%.

5.References:

[1] Baliga V, Sapsford R. Diabetes mellitus and heart failure—an overview of epidemiology and management. Diabetes & Vascular Disease Research. 2009, 6(3):164-171.

[2] Junttila MJ, Barthel P, Myerburg RJ, et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes, Heart Rhythm. 2010;7(10):1396-1403.

[3]Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldmanmd AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult : executive summary. Circulation.2001; 104 : 2996–3007.

[4]Gutierrez C, Blanchard DG. Diastolic heart failure: challenges of diagnosis and treatment. Am Fam Phys.2004; 69:2609 –2616.

[5] Marwick TH. Diabetic heart disease. Heart.2006; 92: 296–300.

[6] Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care.2001; 24:5 –10.

[7] Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, & Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community. JAMA. 2003; 289:194 –202.

[8]Trinder P. Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. J Clin Pathol. 1969;,22(2):158–161.

[9] Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of two-dimensional echocardiograms. J Am Soc Echocardiogr. 1989; 2(5): 358–367.

[10]Kim WY, Sogaard P, Egeblad H, Andersen NT, Kristensen B(2011): Three-dimensional echocardiography with tissue harmonic imaging shows excellent reproducibility in assessment of left ventricular volumes. J Am Soc Echocardiogr.2011; 14(6): 612–617.

[11] Chan YH. Biostatistics102: Quantitative Data – Parametric & Non-parametric Tests. Singapore Med J. 2003; 44(8): 391-396.

[12]Niklas F Ehl, Michael Kuhne, Miriam Brinkert, Jan Muller-Brand and Michael J Zellweger. Diabetes reduces left ventricular ejection fraction-irrespective of presence and extent of coronary artery disease. European Journal of Endocrinology. 2011;(165) 945–951.

[13]Mustonen JN, Uusitupa MI, Laakso M, Vanninen E, Lansimies E,Kuikka JT & Pyorala K. Left ventricular systolic function in middleagedpatients with diabetes mellitus. American Journal of Cardiology .1994; (73) 1202–1208.

[14]Loimaala A, Groundstroem K, Majahalme S, Nenonen A & Vuori I(2006): Impaired myocardial function in newly onset type 2 diabetes associates with arterial stiffness. European Journal of Echocardiography. 2006; (7) 341–347.

[15]Henry RM, Paulus WJ, Kamp O, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, Bouter LM & Stehouwer CD. Deteriorating glucose tolerance status is associated with left ventricular dysfunction – the Hoorn Study. Netherlands Journal of Medicine. 2008; 66 110–117.

[16] Chatham JC, Seymour AM. Cardiac carbohydrate metabolism in Zucker diabetic fatty rats. Cardiovascular Research. 2002; 55:104–12.

[17]Cai L, Wang Y, Zhou G, Chen T, Song Y, Li X, Kang YJ. Attenuation by metallothionein of early cardiac cell death via suppression of mitochondrial oxidative stress results in a prevention of diabetic cardiomyopathy. J Am Coll Cardiol. 2006; 48:1688–1697.

[18]Petrova R, Yamamoto Y, Muraki K, Yonekura H, Sakurai S, Watanabe T, Li H, Takeuchi M, Makita Z, Kato I, Takasawa S, Okamoto H, Imaizumi Y, Yamamoto H. Advanced glycation endproduct-induced calcium handling impairment in mouse cardiac myocytes. J Molecular Cell Cardiology. 2002; 34:1425–1431.

[19]Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. Circulation Research.. 2006; 98:596–605.

[20]Takimoto E, Champion HC, Li M, Ren S, Rodriguez ER, Tavazzi B, Lazzarino G, Paolocci N, Gabrielson KL, Wang Y, Kass DA. Oxidant stress from nitric oxide synthase-3 uncoupling stimulates cardiac pathologic remodeling from chronic pressure load. J Clinical Investigation. 2005; 115:1221–123

[21]Boudina S, Abel ED. Mitochondrial uncoupling: a key contributor to reduced cardiac efficiency in diabetes. Physiology. 2005; 21:250 –258.

[22]Szabo C. PARP as a drug target for the therapy of diabetic cardiovascular dysfunc¬tion. Drug News Persp,2002; 15:197–205.

[23]Samatha p, Venkateswarlu , siva prabodh v. Lipid Profile Levels in Type 2 Diabetes Melli¬tus from the Tribal Population of Adilabad in Andhra Pradesh, India JCDR. 2012;4302:0012.

[24]Daniel Nii Aryee Tagoe1, and Philip Amo-Kodieh.Type 2 diabetes mellitus influences lipid profile of diabetic patients. Scholars Research Library Annals of Biological Research. 2013; 4 (6):88-92

[25]Durrington P, Sniderman A. Secondary hyperlipidemia. In: Hyperlipidemia. Health Press, Oxford, UK, 2002; 71–89).

[26]Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans. Implications for the insulin-resistant state. Diabetes Care. 1996; 19: 390–393 .

[27] Ahmed AM ,Elinasri HA. Patterns of lipid changes among type 2 diabetes patients in Sudan. Eastern Mediter Health J, 2008; 14:2.