



Cardiac Biomarkers, Lipids and Homocysteine In Type 2 Diabetes Mellitus with and Without Complications.

JAYAKRISHNAN.S.

Department of Laboratory Medicine, SK Hospital, Edappazhinji, Thiruvananthapuram 695006

VIDYA.V

Department of Laboratory Medicine, SK Hospital, Edappazhinji, Thiruvananthapuram 695006

JAYANTHI BAI.N.

Department of Laboratory Medicine, SK Hospital, Edappazhinji, Thiruvananthapuram 695006

ABSTRACT

Diabetes mellitus is a metabolic disease with hyperglycemia whose incidence and prevalence has significantly increased in recent decades. Diabetes mellitus is responsible for micro vascular complications like retinopathy, neuropathy, and nephropathy and cardio myopathy. In the present study the levels of cholesterol ,triglycerides ,glucose, troponin I, and CK MB are significantly elevated in T2DM with cardiovascular complications compared to T2DM. The LDL-C was significantly not altered in male patients but definitely elevated in female T2DM with vascular complications. Further hyperhomocysteinemia is noticed in T2DM with complications as compared to T2DM. Homocysteine is a neglected risk factor but is the major culprit for T2DM and cardiovascular disease. In Indian community there is elevated levels of homocysteine an independent major predictor of T2DM and CAD.

KEYWORDS : Diabetes mellitus, Troponin I, CK-MB, Homocysteine.

INTRODUCTION

India tops the world diabetes list with 31.7 million diabetic patients and this is likely to rise to 79.4 million by the year 2030(1). Over ninety percent of them have type 2 diabetes mellitus (T₂DM) (2). T₂DM patients are frequently prone to atherosclerotic complications which account to more than 80 % of all diabetic mortality (3).

Diabetic patients have 2-4 times higher risk of CAD mortality as compared to the general population (4). Moreover CAD has a few peculiarities in diabetic patients. CAD usually occurs earlier, progresses faster and is more diffuse. CAD also carries higher mortality and morbidity in diabetic patients than the general population (5). Traditional risk factors often do not fully explain higher cardiovascular mortality in T₂DM patients.

Diabetes mellitus is a group of metabolic diseases arising out of derangement of carbohydrate, lipid and protein metabolisms. This is due to hyperglycemia resulting from defects in insulin secretion, insulin action or from both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs like eyes, kidneys, nerves, heart and blood vessels. Diabetes mellitus affecting an estimated 5% to 10% adult population in industrialized countries, Asia, Africa, Canada, America and South America has an adverse impact on society (6).

Dislipidemia is an established risk factor for cardiovascular deaths. The risk is more in T₂DM patients. The contribution of hyperglycemia, diabetic dislipidemia, insulin resistance and hypertension produce and enhance atherogenic environment within the circulation (7). However atherosclerosis occurs in same patients without any of the known risk factor like dislipidemia, smoking, diabetes mellitus or hypertension. This could be attributed to other novel risk factors like homocysteine (8,9).

In T₂DM, low levels of HDL-C indicates an inverse relationship between HDL-C and adverse cardiac events. There is increase in LDL -C which has been recognized as an independent risk factor by National Cholesterol Education Programme [NCEP](10). The increased levels of LDL in turn lead to increased oxidized LDL which contribute to the atherogenicity in the coronary vessels.

Hyperglycemia of T₂DM is prone to result in increased risk of CAD. Increased triglyceridemia results in increased VLDL-C. Increased triglycerides could cause atherogenicity independent of LDL cholesterol. The mechanism of atherogenicity due to increased levels of triglycer-

ides is attributed to the oxidised triglyceride lipoproteins. VLDL is the effective substrate for the free radical reaction and the products could accelerate the progression of the disease. Total cholesterol/HDL-C ratio is higher in T₂DM which is the most powerful predictor of coronary artery disease, rather than the cholesterol and HDL-C levels as such.

Homocysteine(Hcy) is a sulphur containing amino acid which is a metabolic intermediate in the metabolism of the essential amino acid methionine. Homocysteine is elevated in T₂DM which can increase the risk of T₂DM complications like retinopathy, neuropathy, nephropathy and even cardio vascular events. Several studies have shown that the site of adverse effect of Hcy in cardiovascular disease include endothelial surface, vascular smooth muscle cells, connective tissue interaction with plasma lipoproteins and clotting factors.

In westerners hyperhomocysteinemia in diabetic patients has been reported to be much higher than in the community. On the other hand, in Indian diabetic patients, as the incidence of hyperhomocysteinemia in the community itself is high, hyperhomocysteinemia is probably already present when the patient develops diabetes. Hence hyperhomocysteinemia is likely to interact with diabetes from the very beginning and cause greater deleterious effects (11).

MATERIALS

The study consisted of 148 T₂DM patients, half of them (74) males and the other half females (74). Again males and females are divided into 2 groups consisting of 37 T₂DM and 37 T₂DM with complications. All patients were diagnosed as T₂DM by the experts in the diabetic clinic and the T₂DM patients with cardiovascular disease are diagnosed by expert cardiologists of S.K.Hospital.

METHOD

Troponin I, CK-MB and homocysteine by the chemiluminescence microparticle assay using Architect i1000SR.

Total Cholesterol (CHOD POD) Triglycerides by combinations of enzymes Lipoprotein lipase, glucose oxidase and peroxidase.

HDL-C and LDL-C Direct measurement using two reagent formats. Glucose (Hexokinase Method) These are estimated using Dimension X Pand of Siemens.

RESULTS

Table - 1 shows the comparison of biocardiac markers, Lipids and Glucose levels between T2DM with and without complications of

cardiovascular disease .There is significant elevation in Troponin I, CK-MB, Total cholesterol, Triglycerides and Glucose.HDL –C showed a decrease in T₂DM with cardiovascular disease.

In female T₂DM patients with cardiovascular risk there is increase in Troponin-I, CK-MB, Total Cholesterol and LDL-C whereas HDL-C showed a decrease. Further, elevation in Triglycerides and glucose are not significant statistically (Table-2).

Table -3 indicates the levels of homocysteine in T₂DM with and without cardiovascular complication .There are 37 T₂DM and 37 T₂DM with cardiovascular complication. The homocysteine levels are elevated in 81% of T₂DM with complication. The increase is statistically significant.

Homocysteine level in female T2DM with and without cardiovascular diseases is presented in Table -4.As in the case of males the homocysteine levels are elevated in 54% of females with T₂DM complications. The increase is statistically significant.

DISCUSSION

Diabetes mellitus is a metabolic disease associated with hyperglycemia whose intolerance and prevalence have significantly increased in recent decades. The cardio vascular complications of diabetes could be neuropathy, cardiopathy, and microvascular complications (12). This is due to enhanced vascular oxidant stress, generation of reactive oxygen supplies and advanced glycation end products .In T₂DM, hyperglycemia is associated with insulin resistance which is strong independent predictor of cardio vascular disease (13).Insulin resistance leads to dislipidemia, increased LDL susceptibility to oxidation (14) and impaired glucose tolerance .Dislipidemia of T₂DM results in increased plasma TG, decreased HDL-C and increased LDL-C leading to small dense LDL(15).Diabetes mellitus can cause endothelial dysfunction and coagulation (16) which can produce cardio vascular diseases. Cardiovascular diseases are the leading cause of death and morbidity in the world .There are well established risk factors such as hypertension, obesity , smoking and family history for myocardial infarction. T₂DM adds to the risk for cardiovascular mortality (17).

Cardiospecific and sensitive biomarkers play a major role in the diagnosis and prognosis of MI . In the present study dislipidemia, cardiac biomarkers Troponin T ,CK-MB,glucose levels and the strong , independent, graded, modifiable risk factor for MI viz homocysteine are measured and presented in Tables 1-4.The study includes both male and female patients with and without complication of T₂DM.

Male T₂DM patients with complication of cardiovascular disease showed elevated biocardiac markers, cholesterol ,Triglycerides and plasma glucose compared to T₂DM patients having good control of T₂DM.The increase in the above case is statistically significant .A significant decrease in HDL –C in male T₂DM patients with complication(p <0.0001) is also observed. However, LDL-C did not show any appreciable increase.

A comparison of female T₂DM patients with complications showed elevated levels of

Troponin I, CK-MB, Cholesterol and LDL cholesterol .In all these cases the increase is statistically significant. There is a decrease in HDL –C .A marginal increase in glucose level is noticed which is not statistically significant probably due to its wide variation.

T₂DM is associated with both micro and macro vascular complications .Atherosclerosis is a co-morbid condition for T₂DM.Impairment of vascular endothelial function is the initial step in the development of cardiovascular disease .Elevated cholesterol in T₂DM can cause inflammatory response and activation of reactive oxygen species (ROS). Oxidised LDL recognized by macrophages can be converted into foam cells which is an important event in atherogenesis. In the present study there is higher incidence of cardiac disease in T₂DM with complication . Moreover, it is prevalent in males but to a lesser extent in females.

Several studies have shown a positive correlation between glucose intolerance and cardio vascular disease with obesity, dislipidemia, hypertension, smoking , sedentary life style ,poorly regulated T₂DM and hyper insulinemia. However all these factors fail to explain the strong

association of diabetes with premature atherosclerosis .Recently it has been suggested that hyperhomocysteinemia could be an independent risk factor predicting complications in diabetes, especially atherosclerotic events (18).

The European Union Concerted Action Project ,”hyperhomocysteinemia and vascular disease” showed that a plasma homocysteine level of 0.162 mg%, accelerates the risk of MI and cerebral or vascular disease in both men and women .Several studies have revealed that elevated level of Hcy in poorly controlled T₂DM is related to increased risk of atherosclerosis and cardio vascular disease .The increased prevalence of elevated Hcy with macroangiopathy and nephropathy in T₂DM is well demonstrated (19).T₂DM patients have both Hcy and dislipidemia(20).A study in Mumbai by Dr.Talwar clinic observed lowering of risk for cardiovascular disease in T₂DM by poly vitamin therapy(21).

CONCLUSIONS

T₂DM patients in India frequently have both dislipidemia and hyperhomocysteinemia .Both of them accelerate the progression of atherosclerosis .Cardio vascular complications of T₂DM is responsible for 80% of all diabetic mortality .About 2/3rd of these deaths are due to CAD.

Homocysteine levels are high in Indian community and low levels of B₁₂ and folic acid are due to vegetarian diet. Homocysteine elevates diabetes mellitus complications like dislipidemia and progression of cardiovascular disease .Myocardial infarction is the major cause of mortality and morbidity all over the world .Homocysteine is an unnoticed neglected major culprit for T₂DM and its complications .Hence screening of homocysteine from an early age and supplementation with B₆, B₁₂ and folic acid vitamins through fortified food grains could lower the risk of T₂DM and CAD especially in youngsters. This will have a far reaching effect in protecting community health and curbing the expenses of health care professionals and Governments.

Table No-1
Troponin I, CK-MB, Glucose and Lipids in Male T₂DM with and without Complications.

Sl.No	Param-eter	Units	Mean ± SD		p -Value
			Type 2 Diabetes Mellitus(n=37)	Type 2 Diabetes Mellitus with Complications (n=37)	
1	Troponin I	ng/ml	0.027±0.330	5.81±4.241	<0.0001
2	CK-MB	ng/ml	1.213±0.523	22.59±37.16	<0.0008
3	Total Cholesterol	mg/dl	165.70±36.23	191.21±45.69	<0.009
4	Triglycerides	mg/dl	142.32±34.55	172.08±52.58	<0.005
5	HDL-C	mg/dl	39.81±7.58	31.35±3.80	<0.0001
6	LDL-C	mg/dl	135.45±29.83	137.35±38.48	<0.808
7	Glucose	mg/dl	182.4±78.16	221.59±97.03	<0.006

Table No-2
Troponin I, CK-MB, Glucose and Lipids in Female T₂DM with and without Complications.

Sl.No	Parameter	Units	Mean ± SD		p -Value
			Type 2 Diabetes Mellitus(n=37)	Type 2 Diabetes Mellitus with Complications (n=37)	
1	Troponin I	ng/ml	0.032±0.045	2.407±3.45	<0.0001
2	CK-MB	ng/ml	1.018±0.37	12.686±12.909	<0.0001
3	Total Cholesterol	mg/dl	155.78±30.937	216.27±56.96	<0.0001
4	Triglycerides	mg/dl	137.97±32.92	148.37±31.59	<0.185
5	HDL-C	mg/dl	36.62±4.36	32.89±5.48	<0.002
6	LDL-C	mg/dl	118.13±29.522	147.86±21.12	<0.0001
7	Glucose	mg/dl	175.45±65.46	185.75±38.489	<0.414

Table No-3
Hcy Levels in T₂DM Males with and without cardiovascular Diseases.

Sl.No.	Cas-es	Elevat-ed Hcy No.	%	Hcy (µm/L)		p Value
				T ₂ DM	T ₂ DM with Complications	
1	37	30	81	9.53±0.719	20.899±3.907	<0.0001

Table No-4
Hcy Levels in T₂DM Females with and without cardiovascular Diseases.

Sl.No.	Cas-es	Elevat-ed Hcy No.	%	Hcy (µm/L)		p Value
				T ₂ DM	T ₂ DM with Complications	
1	37	20	54	7.027±2.509	15.885±3.478	<0.0001

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