Gender specific utility of lipid ratios and its correlation with systemic inflammation in acute myocardial infarction (AMI) patients with type 2 diabetes mellitus – A hospital based study

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Abstract

Objective: To evaluate Gender specific alterations in the levels of serum lipid profile parameters Total Cholesterol (TC), Triglycerides (TG), Low density lipoprotein Cholesterol (LDL-C), High density lipoprotein Cholesterol (HDL-C), non-HDL-C (TC-HDL-C), lipid ratios [TC/HDL, TG/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL], hs-CRP and uric acid in male and female siabetic patients with Acute Myocardial Infarction(AMI) compared to male and female siabetic patient controls, and to correlate the serum lipid ratios with serum hs-CRP and uric acid levels among male and female Type 2 DM patients with AMI.

Materials and Methods: Blood samples collected after admission from thirty male and thirty female Type 2 DM with AMI, and from thirty male and thirty female Type 2 DM patients with no previous history of coronary heart disease as controls, the samples were analyzed for levels of serum lipid profile, hs CRP and uric acid.

Results: There was a significantly high TG/HDL ratio in males diabetic patients $p<0.05$, and no significant difference in lipid profile parameters, lipid ratios, hs-CRP and uric acid levels among female & male siabetic patient controls, in female diabetic patients with AMI the levels of TC, HDL, TG & Lipid ratios TC/HDL, non HDL/HDL was significantly higher $p<0.05$. None of the lipid ratios correlated with the increase in hs-CRP levels and the mean levels of uric acid was within the normal range in both the groups.

Conclusion: A higher level of dyslipidemia in female diabetic patients with AMI compared to male diabetic patients with AMI necessitates the need to initiate a more aggressive lipid management strategy for women with diabetes. Estimating the serum hs CRP levels as independent parameter may serve as predictor of risk of AMI irrespective of their gender during routine follow up of diabetic patients.

Keywords: Diabetes mellitus, Acute myocardial Infarction, Gender, Lipid ratios, hs-CRP, Uric acid.

Introduction

The prevalence of diabetes mellitus is increasing drastically. And the patients with diabetes are at increased risk of developing atherosclerosis which leads to coronary artery disease. The lethal manifestation of Coronary Heart Disease (CHD) is myocardial infarction, that may result in sudden death.[1] Compared to age-matched non-diabetic women, women with Type 2 DM exhibit several fold higher rates of death related to coronary artery disease irrespective of their menopausal state, identical to the death rates observed in Type 2 DM men. Among the various risk factors known, impaired lipid metabolism is one of the crucial risk factors in the development of AMI in Type 2 DM. Though genetics play a role in the regulation of lipid metabolism to a certain extent, its levels in the circulation can still be modified.

The management of dyslipidemia after myocardial infarction is an important aspect of post-myocardial infarction care.[2,3] Several studies have observed a significantly higher Total cholesterol and Triglyceride levels and lower (HDL-C) levels in AMI patients. There is evidence that the LDL-C/HDL-C ratio continues to be a valuable and standard tool to evaluate cardiovascular disease (CVD) risk in all populations, as compared to levels of apolipoprotein (apo) B and the ratio of apo B/apo A-I which are supposed to be more accurate predictors of CVD risk.[4] Few studies have observed cardiovascular events in patients with low levels of HDL, despite having normal LDL-cholesterol levels. Similarly, individuals with high concentrations of non-HDL cholesterol, remain at increased cardiovascular risk.[5] Studies with respect to the pattern of lipid abnormalities among the gender groups especially with regard to lipid ratios in AMI patients with type 2 diabetes mellitus are very few, thus there is a need for such studies that would throw some light on gender specific lipid abnormality for the risk assessment of myocardial infarction in these patients.

Hence, the present study was undertaken to evaluate alterations in the lipid profile, lipid ratio levels in male and female AMI patients with Type 2 Diabetes mellitus, compared with male and female Type 2 Diabetes mellitus with no previous history of coronary heart disease. To correlate the lipid ratios with hs-CRP and uric acid among male and female Type 2 Diabetes mellitus patients with AMI. This is in order to achieve effective preventive and disease management strategies

to reduce CVD risk associated with Type 2 DM among male and female subjects.

Materials and Methods

The present study was conducted at Sri RL Jalapa hospital and Research centre attached to Sri Devaraj urs medical college following approval by the Central ethics committee. The study was conducted between 2015 -2017. Study included patients aged between 30-60yrs. The study subjects were grouped as Group I & Group II.

Group 1: 30 male and 30 female patients with Type 2 Diabetes mellitus admitted at RLJH-NH heart centre with chest pain and diagnosed as case of Acute MI by the treating cardiologist on the basis of clinical examinations and ECG findings.

Group 2: 30 male and 30 female age and sex matched type 2 diabetes mellitus patients without any history of Coronary heart disease were included as controls.

Exclusion Criteria: Patients with chest pain due to any cause other than MI, with history of any recent surgery/active infections/chronic inflammatory diseases/renal dysfunction and malignancy/Liver disease/ Hemoglobinopathies, were excluded from the study.

After obtaining the informed consent, under complete aseptic precautions five milliliters of Fasting Blood sample after an overnight fast was collected in appropriate vaccutainer tubes from the study subjects, Blood Samples in Red Vaccutainer was centrifuged at 3000 rpm for 5mins and the serum separated was stored at 4^0C. The Serum separated was analyzed for Serum hs-CRP mg/L[6] (<1mg/L), Serum uric acid mg/dL[7,8] (2.6-7.2 mg/dL), Serum lipid profile includes Total Cholesterol TC mg/dL[9] (120-200 mg/dL), Triglycerides TG mg/dL[10] (44-150 mg/dL) High Density Lipoprotein-C HDL-C mg/dL[11] (40-60 mg/dL), Low Density Lipoprotein –C LDL-C mg/dL (100-129 mg/dL) (calculated as (Total cholesterol) – (High-density lipoprotein cholesterol [HDL-C]) – (triglycerides/5) in mg/dL)[12] using Vitros 5.1FS dry chemistry autoanalyzer, and the lipid ratios (TC/HDL, TG/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL) were calculated. Sample collected in EDTA vaccutainer was analyzed for HbA1C (%) using BIO RAD D10 HPLC autoanalyzer, and the sample collected in fluoride vaccutainer was analyzed for Fasting Blood glucose levels[13] using Vitros 5.1 FS Dry chemistry autoanalyzer.

Statistical Analysis

The data was analyzed by SPSS version 20 software. Quantitative data were expressed as mean ±standard deviation and the significance of the difference between male and female Acute MI patients with Type 2 Diabetes mellitus and controls was analyzed by Student's *t* test. Pearson correlation was done to establish the relationship between quantitative variables (lipid ratios, Uric acid and hs-CRP).p value <0.05 will be considered as statistically significant.

Results

The Table 1 shows the difference in the mean levels of Total Cholesterol, HDL, TG & Lipid ratios TC/HDL, non HDL/HDL and uric acid in female diabetic patients with AMI to be statistically significant compared to male diabetic patients with AMI. Further the Total Cholesterol, HDL, TG levels are found to be much higher in female diabetic patients with AMI than the male diabetic patients with AMI. However there was no statistically significant difference in the levels of LDL, non-HDL-C, TG/HDL, LDL/HDL, LDL/non HDL, hs CRP in female diabetic patients with AMI compared to the Male diabetic patients with AMI. Table 2 shows no statistically significant difference with respect to the lipid profile, lipid ratios and the pro inflammatory markers between female & male diabetic patient controls, except for TG/HDL ratio (13.74±8.29) & (19.00±10.11) in female and male diabetic patients respectively, is observed to be higher in male diabetic patient group as compared to female diabetic patient group. Table 3 shows the difference in the Mean levels of serum lipid profile parameters [TC, LDL-C, & non-HDL-C] & lipid ratios [TC/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL] among the control subjects to be statistically significant and at higher levels in female diabetic patient control group as compared with female Type 2 diabetic patient with AMI. However the levels of hs CRP alone are found to be higher in female Type 2 diabetic patient with AMI than the female diabetic patient control. Further there was no significant difference in the levels of serum HDL, TG, the lipid ratio (TG/HDL) & uric acid between the Group I & Group II Subjects. Table 4 shows the Mean levels of serum lipid profile parameters [TC, TG, LDL-C, uric acid non-HDL-C,] & the lipid ratios [TC/HDL, TG/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL] to be significantly higher in Male Type 2 Diabetes mellitus control group compared to Male Type 2 Diabetes mellitus patients with AMI. However the levels of hs-CRP are higher among Male Type 2 Diabetes mellitus patients with AMI than Male Type 2 Diabetes mellitus control group. There was no significant difference in the levels of HDL-C between the both the groups. Table 5 shows that there is no significant correlation of lipid ratios with hs-CRP among the Group I female and male diabetic patients with AMI. Table 6 shows that there was no significant correlation of lipid ratios with uric acid among Group I female and male diabetic patients with AMI.

Table 1: Comparison of lipid profile parameters, lipid ratios, hs CRP & uric acid among group I female diabetic patients with AMI & group I male diabetic patients with AMI

Parameter	Group I Female n = 30 Mean ± SD	Group I Male n = 30 Mean ± SD	P-Value
T. Chol	119.97±42.819	94.30±43.150	0.024*
HDL	21.87±10.763	14.20±8.735	0.004*
TG	221.23±95.687	148.70±75.386	0.002*
LDL	55.25±24.841	55.85±33.775	0.941
hs CRP	17.30±19.761	18.00±23.393	0.901
Uric acid	4.10±0.960	5.07±2.016	0.021*
non-HDL-C	98.10±35.822	80.10±36.784	0.060
TC/HDL	6.19±2.04	7.89±3.24	0.018*
TG/HDL	11.23±3.85	13.29±7.07	0.165
LDL/HDL	2.58±1.68	3.75±2.73	0.051
non HDL/HDL	5.19±2.04	6.89±3.24	0.018*
LDL/non HDL	0.50±0.19	0.54±0.26	0.465

*P Value < 0.05 is significant

Table 2: Comparison of lipid profile parameters, Lipid ratios, hs CRP & uric acid among group II female diabetic patient controls & group II male diabetic patient controls

Parameters	Group II Female (n= 30 Mean ± SD	Group II Male (n= 30 Mean ± SD)	P-Value
T. Chol	147.07± 35.99	155.58 ±44.33	0.409
HDL	19.93 ±11.86	17.21 ±11.18	0.352
TG	210.90 ±72.61	248.73 ± 88.69	0.070
LDL	84.93 ±34.51	89.64±34.19	0.589
hs CRP	4.10±3.72	3.45 ±4.69	0.550
Uric acid	3.73 ±2.26	3.30 ±1.38	0.360
non-HDL-C	127.13 ±38.13	138.36 ±40.26	0.261
TC/HDL	9.18±4.37	11.22±4.32	0.067
TG/HDL	13.74±8.29	19.00±10.11	0.028*
LDL/HDL	5.44±3.22	6.48±2.77	0.175
non HDL/HDL	8.18±4.37	10.22±4.32	0.067
LDL/non HDL	0.65±0.15	0.64±0.11	0.732

*P Value < 0.05 is significant

Table 3: Comparison of lipid profile parameters, hs CRP & uric acid among group I female diabetic patients with AMI and group ii female diabetic patient controls

Parameters	Group I Female (N=30 Mean ± SD)	Group II Female (N=30 Mean ± SD)	P-Value
TC	119.97±42.819	147.07± 35.99	0.010*
HDL	21.87±10.763	19.93 ±11.86	0.511
TG	221.23±95.687	210.90 ±72.61	0.639
LDL	55.25±24.841	84.93 ±34.51	0.001*
hs CRP	17.30±19.761	4.10±3.72	0.001*
Uric acid	4.10±0.960	3.73 ±2.26	0.416
non-HDL-C	98.10±35.822	127.13 ±38.13	0.004*
TC/HDL	6.19±2.04	9.18±4.37	0.001*
TG/HDL	11.23±3.85	13.74±8.29	0.138
LDL/HDL	2.58±1.68	5.44±3.22	0.001*
non HDL/HDL	5.19±2.04	8.18±4.37	0.001*
LDL/non HDL	0.50±0.19	0.65±0.15	0.001

*P Value < 0.05 is significant

Table 4: Comparison of lipid profile parameters, hs CRP & uric acid among group I male diabetic patients with AMI and group II male diabetic patient controls

Parameters	Group I Male n=30 Mean ± SD	Group II Male n=30 Mean ± SD	P-Value
TC	94.30±43.150	155.58 ±44.33	0.001*
HDL	14.20±8.735	17.21 ±11.18	0.271
TG	148.70±75.386	248.73 ± 88.69	0.001*
LDL	55.85±33.775	89.64±34.19	0.001*
hs CRP	18.00±23.393	3.45 ±4.69	0.001*
Uric acid	5.07±2.016	3.30 ±1.38	0.001*
non-HDL-C	80.10±36.784	138.36 ±40.26	0.001*
TC/HDL	7.89±3.24	11.22±4.32	0.001*
TG/HDL	13.29±7.07	19.00±10.11	0.011*
LDL/HDL	3.75±2.73	6.48±2.77	0.001*
non HDL/HDL	6.89±3.24	10.22±4.32	0.001*
LDL/non HDL	0.54±0.26	0.64±0.11	0.037*

*P Value < 0.05 is significant

Table 5: Correlation of lipid ratios with hs-CRP among group I female diabetic patients with AMI and group I male diabetic patients with AMI

Parameters	Group I Female		Group I Male	
	r-Value	P-Value	r-Value	P-Value
TC/HDL	-0.017	0.927	-0.226	0.229
TG/HDL	0.110	0.562	-0.159	0.402
LDL/HDL	0.052	0.787	-0.095	0.617
Non HDL/LDL	-0.017	0.927	-0.226	0.229
LDL/non-HDL	0.133	0.484	0.043	0.820

Table 6: Correlation of lipid ratios with Uric acid among Group I female diabetic patients with AMI and Group I male diabetic patients with AMI

Parameters	Group I Female		Group I Male	
	r-Value	P-Value	r-Value	P-Value
TC/HDL	-0.134	0.480	-0.330	0.075
TG/HDL	0.089	0.640	-0.293	0.116
LDL/HDL	-0.007	0.969	-0.205	0.277
Non HDL/LDL	-0.134	0.480	-0.331	0.075
LDL/non-HDL	0.083	0.663	-0.070	0.712

Discussion

Diabetes causes dyslipidemia which is responsible for the greater risk of morbidity and mortality in Type 2 diabetes mellitus patients.[14] Studies have found that women have a certain significant difference in lipid and lipoprotein profiles than men. The present study aimed to evaluate the effect of gender on the various basic lipid profile parameters, lipid ratios, hs CRP and uric acid in diabetic patients and correlate the levels of lipid ratios with serum hs CRP and uric acid which are the recent non traditional markers in the risk assessment of Acute Myocardial Infarction in these patients. In order to achieve effective preventive and disease management strategies to reduce CVD risk associated with T2DM among males and females.

The National Cholesterol Education Programme (Adult Treatment Panel III) guidelines recommends an LDL of <100 mg/dl, a Total cholesterol levels of <200 mg/dl, and an HDL cholesterol level of >45 mg/dl in men and >55 mg/dl in women as optimum.[15,16] In our study we observed the Total Cholesterol, TG, non-HDL-C levels to be higher than the recommended levels in male diabetic patients as compared to female diabetic patients, but the difference was not statistically significant, the study done by Rokshana Yeasmin et al also observed an increase in TG levels in male as compared to female diabetic patients, however their study found the levels of TC and LDL-C to be increased in female diabetic patients in comparison to males. Further in our study LDL –C levels in both the groups remained the same.[17]

Among the lipid ratios TG/HDL was observed to be higher in male diabetic patient group as compared to female diabetic patient group. This difference could be due to a higher HDL levels seen in female patients as compared to the male diabetic patients or due to a higher TG levels observed in male diabetic patients as compared to female patients, since the difference in the

levels of HDL and TG among the male and female diabetic patients are not statistically significant, the significance of the ratio TG/HDL in the risk assessment of cardiovascular complications in these patients needs to be tested considering larger sample. The lipid ratios TC/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL did not show any statistically significant changes between males and female diabetic patients.

Further, on comparing the mean levels of the lipid parameters among the gender group in diabetic patients with AMI, it was observed that the female diabetic patients with Acute Myocardial Infarction showed significantly higher levels of Total Cholesterol, TG as compared to the Male diabetic patients with AMI, the lipid ratios TC/HDL, non HDL/HDL was significantly higher in males as compared to female diabetic patients with AMI, this may be because the HDL levels was significantly higher in females as compared to males. However as the lipid levels was higher than the recommended levels and even HDL was lower than the optimum levels as per the recommended guidelines, it predicts that female diabetic patients are at a higher risk as compared to males. These findings are in par with the study findings of Xiaomei Zhang et al, Supriya Bajaj et al.[18,19]

The reduced serum HDL levels may be a reasonable lipid disorder in diabetic patients with AMI apart from the significance of association of lipid profile with acute myocardial infarction. The protective action of estrogen, on the cardiovascular system and in suppressing obesity and dyslipidemia may be decreased in female patients with diabetes.[20] On further comparing the lipid profile and lipid ratios within the groups we observed the mean serum lipid profile levels of Total Cholesterol, LDL-C, and Non-HDL-c and the lipid ratios (Total Cholesterol/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL) in female type 2 diabetes mellitus patients was at higher levels as compared to female Type 2 Diabetes mellitus with AMI. Similarly the mean serum lipid profile levels of TC, TG, LDL & non-HDL-C and lipid ratios TC/HDL, TG/HDL, LDL/HDL, non HDL/HDL, LDL/non HDL in Male diabetic patients were higher as compared to Male diabetic patients with AMI.

High sensitive C-reactive protein (hs-CRP), is a acute phase protein produced by hepatocyte cell, which is considered earlier as the inflammatory biomarker and has been reported to be associated with both diabetes and CAD.[21] The American Heart Association & Centre for Disease Control Working Group on markers of inflammation in Cardiovascular Disease has classified serum hs-CRP levels <1 as low, 1–3 intermediate and >3 mg/l as high-risk groups for global CVD, respectively.[22] Hyperuricemia is a metabolic abnormality that is closely associated with obesity and type 2 diabetes.[23] Hyperuricemia is related to endothelial dysfunction by inducing anti-proliferative effects on endothelium and impairing nitric oxide production and inflammation, through increased C-reactive protein expression.[24] Our study observed the mean levels of serum hs-CRP to be >3 mg/L (4.10±3.72 mg/L) &(3.45±4.69 mg/L) in female and male diabetic patients respectively and the levels were quiet higher compared to controls (17.30±19.761 mg/L)& (18.00±23.393 mg/L) in female and male diabetic patients with AMI, suggesting that irrespective of the gender the diabetic patients are at an increased risk for CVD. Studies by Lima et al, Joshi et al & Munilakshmi et al have shown similar findings.[25-27] However the uric acid levels were within the normal range of 2-6 mg/dl and it did not correlate with any of the lipid profile parameters or lipid ratios in both the gender groups.

Conclusion

Our study observed a higher dyslipidemia in female diabetic patients with AMI as compared to males which necessitates the need to initiate more aggressive lipid management strategies for diabetic women in order to overcome the gender imbalances. Although this dyslipidemia is a for runner of chronic low grade inflammation it is not found to correlate significantly with the sensitive marker of systemic inflammation hs CRP, even though there was a reduction in the levels of TC, TG, Non HDL cholesterol in diabetic patients with AMI as compared to the diabetic patients without cardiovascular complications, suggests that the levels of lipid parameters does not prevent the risk of developing an AMI in a diabetic patient. Further the levels of hs CRP was found to be significantly increased above the high risk levels in the diabetic patients with AMI in both the gender groups, this reflects a subclinical low grade inflammation and strongly predisposes these individuals to AMI in near future. Since none of the lipid profile parameters or lipid ratios except for Non HDL-C in female diabetic patients with AMI correlated with the levels of hs CRP, we can emphasize the importance of estimating the levels of serum hs CRP as a independent parameter during routine analysis and follow up of lipid profile analysis among the diabetic patients for the prediction of risk of AMI irrespective of the gender.

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Conflict of Interest: All authors have none to declare.

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