Non cardiac parameters and their importance in the progression of myocardial ischemia and acute myocardial infarction

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Abstract

Introduction: The morbidity and mortality of acute myocardial infarction is rampantly growing worldwide. The infiltration of oxidised lipoproteins in intima of artery results in myocardial ischemia and ends up in AMI if not treated. Thus, the evaluation of risk factors will helps in understanding the ischemia and its progression towards infarction.

Materials and Method: Three groups, control (n=33), ischemia (n=38) and infarction (n=42) were included. The parameters FBS, urea, creatinine, lipid profile and liver function tests were carried out.

Results: All the data seen as mean ± SE. The mean were analysed by (ANOVA) with a post hoc multiple comparison test of student Newman Keuls test. The mean difference was considered as significant at <0.05. The FBS and creatinine, triglycerides and total cholesterol were significantly differed in infarction when compared to control and ischemia. The serum levels of liver enzymes were significant in infarction in comparison to control but no difference was observed between ischemic group and control.

Conclusion: Patients with increased levels of FBS, TAG, LDL and liver enzymes tend to have an increased risk of ischemia and infarction. Therefore in the current study, the assessment of non-cardiac parameters helps to understand the influence on progressive increase of ischemia and infarction compared to healthy individuals as risk factors.

Keywords: Ischemia, Infarction, Non cardiac markers and Cardiac Markers.

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Introduction

Myocardial ischemia is an increasing health burden. It is caused by the infiltration of lipoproteins in the intima of the coronary arteries resulting in the narrowing of blood vessels known as atherosclerosis. The partial occlusion results in decreased blood flow and hence there will be less oxygen (and nutrients) supply, known as ischemia. The myocardial ischemia if not treated and progression arrested will eventually manifest as a full blown major medical emergency. The risk factors like diabetes mellitus, hypertension, less physical activity, smoking and hyperlipidemia are contributory to the cause and increased risk of coronary impairment directly or indirectly. Further, several studies have claimed genetic pre disposition as one of the cause. However, this depends on demographic variation. It is anticipated that CAD alone will be the prime cause of mortality by 2020 because of the disease severity.(1) Hence prompt diagnosis and treatment are mandatory to reduce this burden.

The major purpose of the present study is to assess the progressive increase of ischemia and infarction by evaluating the influence of non cardiac parameters as risk factors.

Materials and Method

Participants: The present study was carried out at Maharajah's Institute of Medical Sciences (MIMS), India and approved by Institutional (MIMS) Ethics Committee. The participants were enrolled in the present study after acquired the informed consent and three groups i.e., control group, ischemia and AMI group were included.

Inclusion criteria and exclusion criteria: The subjects of both the genders with an age group ranging from 31 to 70 were involved in the present study. All documented myocardial ischemia and AMI cases with no prior history and treatment for cardiac ailments were included in the study. The inclusion criteria was based on parameters like age, sex, life style, family history and also included risk factors like smoking, obesity, hypertension and dyslipidemia. The patients with renal failure, diabetes mellitus, pregnancy, arrhythmias, acute heart failure, myocarditis, old AMI patients, left ventricular hypertrophy, muscular dystrophy and infectious diseases like HIV, hepatitis were excluded.

In this comparative cross sectional study**,** 38 ischemic and 42 infarction participants who came for check up were all included for this study. For the control group 33 participants who visited the hospital for routine health check up and devoid of cardiac problems during the same period were included. The control group included healthy subjects (n = 33) of either sex, who were not suffering from any sort of cardiac illness and the Ischemic subjects (with no past history of ischemia or treatment) of either sex were selected for the study(2) and these participants were corroborated by cardiologist as ischemic cases. The

infarction group of participants (n = 42) was selected from persons of either sex, who were admitted to ICU and the selection of cases based on diagnostic criteria for myocardial infarction according to European Society of Cardiology (ESC), the American College of Cardiology (ACC) and the World Health Organisation (WHO). The blood sample was collected immediately after the admission to ICU of MIMS (within 2 to 3 hours after the onset of myocardial infarction) and the serum was separated.

Biochemical parameters: After preliminary screening for HIV and HbsAg, all the blood samples of controls, ischemia and AMI groups were centrifuged for 10 minutes at 3000 rpm within an hour and the serum was obtained.[3] The serum was preserved at -70º C with necessary precautions till analysis. The serum was analysed for various biochemical parameters in the laboratory as per the guidelines provided in the respective tests and assessed. Turbochem 100 fully automated analyser and humalyser 3000 were used. The serum fasting glucose, blood urea, serum creatinine and lipid profile, total and direct bilirubin kits were acquired from Transasia erba diagnostics. The liver enzyme kits were supplied by Excel diagnostics. The FBS was analysed by glucose oxidase and peroxidise method (GOD-POD).[4] The blood urea was estimated by glutamate dehydrogenase urease method.[5] The serum creatinine was estimated by Jaffe's method and the serum total cholesterol was estimated by cholesterol oxidase and peroxidase method (CHOD-POD).[6] Serum triglyceride was estimated by Trinder method. The HDL cholesterol was analysed by Phosphotungstic Acid Method.[7] Chylomicrons, LDL and VLDL are precipitated from serum by phosphotungstate in the presence of divalent cation such as magnesium. The HDL cholesterol remains unaffected in the supernatant and is estimated with enzymatic cholesterol method. The serum LDL cholesterol and serum VLDL cholesterol were measured by indirect method in accordance with Friedewald formula. The serum bilirubin was estimated by diazo method.[8] The liver enzymes viz., serum aspartate transminase (AST)[9] and serum alanine transminase (ALT)[10] were estimated by International Federation of Clinical Chemistry (IFCC) method. Alkaline phosphatase (ALP) was estimated by Lowry et al, method.[11]

Statistical analysis: All the data were expressed as mean ± SE. The mean were analysed by one way analysis of variance (ANOVA) with a post hoc multiple comparison test of student Newman Keuls test. For all the statistics and graph potting, SigmaPlot 12.0 (Systat software, USA) was used. P <0.05 was considered as significant.

Results

In the present study, the serum values of the non-cardiac biochemical parameters of ischemia and infarction groups were compared with those of control group. Table 1 shows the age wise distribution of control and the experimental groups i.e., ischemia and infarction groups respectively. When compared to the control, the maximum number of cases was registered in the age group of 51 to 60 years in both the experimental groups. The mean age in the control group was 51, in the ischemic group were 53 and in the infarction group was 58 years respectively. The male and female incidence of ischemia and infarction was depicted in Table 2. The incidence of ischemia and infarction is more in male when compared to female and the interesting feature is that the percentage of female incidence (36.8%) in ischemia is more when compared to infarction (11.9%).

The results of FBS, blood urea and serum creatinine estimation were depicted in Fig. 1. It was found that the FBS levels were found to be significantly increased in both the ischemic (97.13 ± 1.00 mg/dL) and infarction groups (103.31 ± 1.52 mg/dL) with respect to control group (92.97 ± 1.15 mg/dL). By comparing the ischemic group with that of infarction group, a significant elevation of serum FBS level was seen among infarction group. Since all the participants from all the three groups (control, ischemia and infarction) were from non diabetic subjects and the values obtained were found to be within the normal range (70 mg/dL to 110 mg/dL). However, the observations indicated that the variation of FBS values were statistically significant amongst all the groups (F=16.569; P <0.001). Nonetheless, significant variations in the values of blood urea were noticed between control group (34.58 ± 1.18mg/dL), ischemia (35.63 ± 0.99mg/dL) and infarction groups (37.55 ± 0.87mg/dL) (F=2.285; P=0.107). The serum creatinine showed significant variation between control (1.03 ± 0 .02mg/dL) and experimental groups (1.09 ± 0.02 mg/dL and 1.11 ± 0.02 mg/dL). There was a slight increase of creatinine in infarction group in comparison to ischemic group, but statistically not significant (F=4.078; P=0.020).

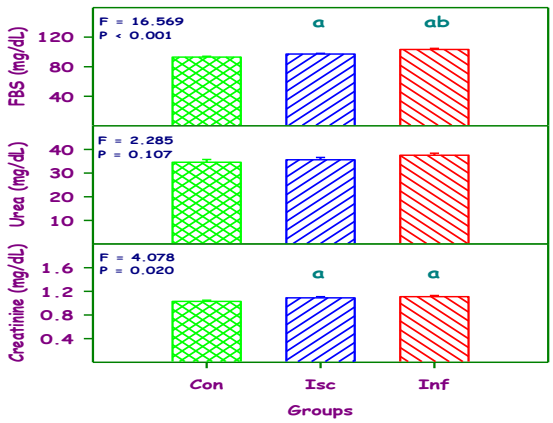

Fig. 1: The serum levels of fasting blood glucose (FBS), urea and creatinine of control (Con),

ischemia (Isc) and infarction (Inf) group participants. Mean ± SE (n – con = 33, Isc = 38 and inf = 42)

a. Significantly different from control group.
b. Significantly different from ischemia group

Serum lipid profile estimation is considered as a diagnostic test to determine the risk of CAD. The observations of total cholesterol and triglycerides were depicted in Fig. The values of total cholesterol in control were 180.69 ± 5.89 mg/dL, in ischemia, 227.18 ± 4.79 mg/dL and in infarction, 256.57 ± 5.33 mg/dL. Observations indicated that there is a significant difference of total cholesterol amongst all the groups (F=49.969; P<0.001). The values of serum triglycerides in ischemia and in the infarction groups were found to be 190.55 ± 5.73 mg/dL and 180.62 ± 6.38 respectively. The values were found to be significant in comparison to control (147.88 ± 7.77 mg/dL). But there was no statistical difference observed between ischemia (B) and infarction (C) groups (F=10.597; P<0.001).

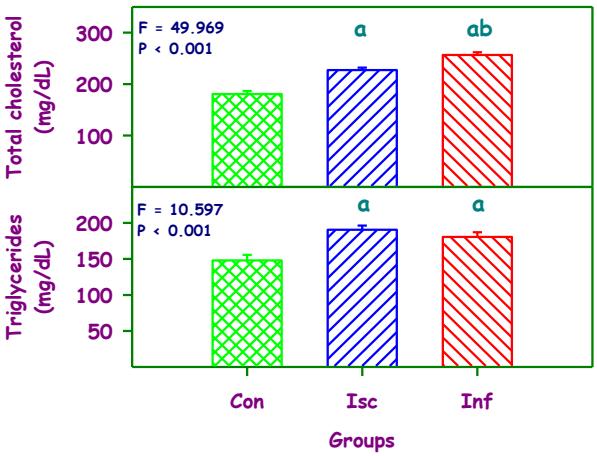

Fig. 2: The serum levels of total cholesterol and triglycerides of control (Con), ischemia (Isc) and infarction (Inf) group participants. Mean ± SE (n – con = 33, Isc = 38 and inf = 42)

a. Significantly different from control group.
b. Significantly different from ischemia group

The serum levels of lipoproteins (HDL, LDL and VLDL) in all the groups have been represented in the Fig. 3. HDL, considered as good cholesterol, showed significant variation in ischemic group (35.66 ± 0.67 mg/dL) in comparison to control (38.26 ± 0.79 mg/dL) (F=5.517; P=0.005). But, it is quite interesting that, there is no statistical variation between control and infarction groups (39.48 ± 0.84 mg/dL), as well as ischemia and infarction groups. The main cause of the CAD is LDL and showed a marked variation in all the three groups A, B and C (112.21 ± 5.11 mg/dL, 151.79 ± 4.05 mg/dL and 172.81 ± 4.43 mg/dL) (F=44.732; P<0.001). The serum levels of VLDL showed a marked variation in ischemia 39.58 ± 1.22 mg/dL and infarction (40.12±1.48 mg/dL) when compared with control (29.76 ± 1.55 mg/dL). The ischemia and infarction group did not show any significant difference.

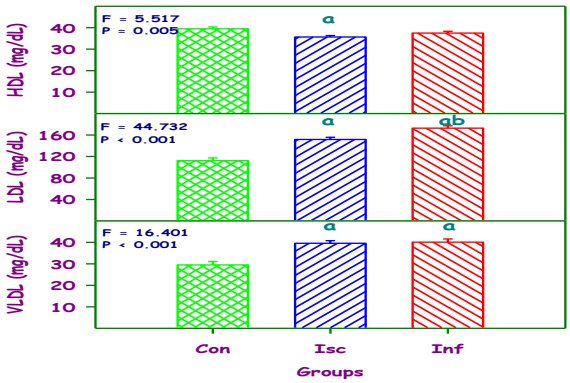

Fig. 3: The serum levels of high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) of control (Con), ischemia (Isc) and infarction (Inf) group participants. Mean ± SE (n – con = 33, Isc = 38 and inf = 42)

a. Significantly different from control group.
b. Significantly different from ischemia group.

Among the liver function parameters, the serum levels of total and direct bilirubin (TB and DB) were depicted in Fig. 4. In comparison to control (0.96 ± 0.02 mg/dL), the TB showed a significant variation in the ischemia (1.02 ± 0.02 mg/dL) and infarction group (1.22 ± 0.93 mg/dL) (F=4.967; P=0.009). There is no significant difference of TB in the ischemia and infarction group. In case of DB, there are no significant variations (F=0.165; P=0.848) between control 0.40 ± 0.13 mg/dL, and experimental groups B and C (0.39 ± 0.01 and 0.35 ± 0.01 mg/dL).

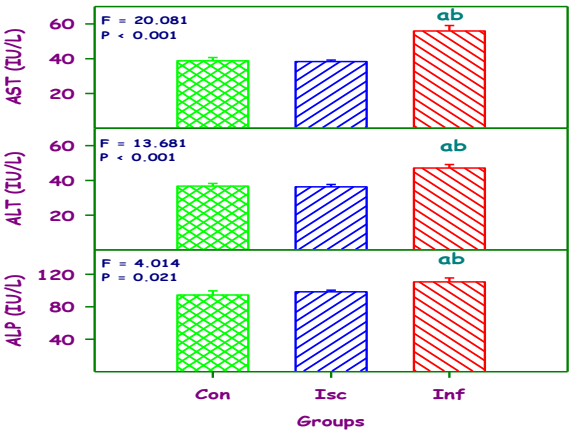

Fig. 4: The serum levels of total bilirubin and direct bilirubin of control (Con), ischemia (Isc) and infarction (Inf) group participants. Mean ± SE (n – con = 33, Isc = 38 and inf = 42)

a. Significantly different from control group.
b. Significantly different from ischemia group

The serum levels of liver enzymes (AST, ALT and ALP) measured in control and experimental groups were represented in Fig. 5. In comparison to the control 38.79 ± 1.91 IU/L, the AST in ischemia group (38.34 ± 0.87 IU/L) did not show any significant variation. However there is marked variation between ischemia and infarction and control and infarction group 55.95 ± 3.14 IU/L (F=20.081; P<0.001). The infarction group registered significant increase of serum ALT (47.14±2.00 IU/L) in comparison to the control (36.73 ± 1.53 IU/L). But there is no difference observed in that of control and ischemia (36.32 ± 1.37 IU/L). At the same there is significant difference is observed between ischemia and infarction group (F=13.681; P<0.001). For ALP, in comparing to control (94.55 ± 5.06 IU/L) the infarction group showed significant variation (110.64 ± 4.92 IU/L). There is statistical variation between ischemia and infarction but not in ischemia (95.45 ± 2.04 IU/L) and control (F=4.014; P=0.021).

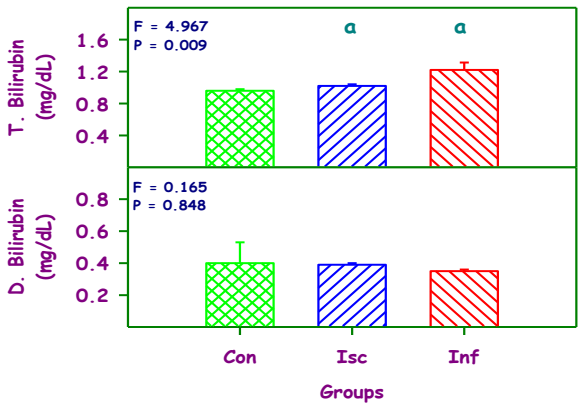

Fig. 5: The serum levels of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) of control (Con), ischemia (Isc) and infarction (Inf) group participants. Mean ± SE (n – con = 33, Isca = 38 and infarction = 42)

a. Significantly different from control group.
b. Significantly different from ischemia group.

Discussion

In the present study, the maximum number of ischemia and infarction cases was seen in the age group of 51 to 60 years. The incidence of ischemia and infarction in female is less in comparison to male. Studies reported that, the average age at first myocardial infarction (MI) is 64.5 years for men and 70.3 years for women. However, coronary artery disease (CAD) was primarily considered a "man's disease," but the incidence is gradually increasing in female too, especially women with hypertension and diabetes. Increased triglycerides carry more risk of causing CAD in women than men.[12] Studies claimed that, in comparison to men there is lesser incidence of CAD before 65 years in women due to cardio-protective role of estrogen.[13]

In the present study, the comparison of non-cardiac parameters was made between control, ischemia and infarction groups. The serum FBS levels differed significantly in ischemia and infarction groups. The studies showed hyperglycemia in angina pectoris (ischemia) worsening the angina further.[14] Studies have reported that stress hyperglycemia may be a marker for severe MI but still it is inconclusive. The increased blood glucose during AMI is due to a compromised metabolic state which leads to rise of catecholamines and reduced insulin sensitivity. It was found that, the FBS provides greater incremental prognostic information than the level at the time of admission. Studies reported that HbA1C is reliable biomarker for the estimation of blood sugar, but the assessment of FBS is not less to HbA1C in assessing the condition promptly. Furthermore, fasting glucose remained an independent predictor of long-term mortality in non diabetic patients.[15] Hyperglycemia contributes to the production of reactive oxygen species (ROS) and consequent oxidative stress. Hyperglycemia and insulin resistance increases the lipolysis and free fatty acids generation (in excess) which are toxic to ischemic myocardium. This result in damage of cardiac myocyte membranes and cause calcium overload that finally reduce myocardial contractility and induce arrhythmias followed by heart failure, hence a poor outcome. Hyperglycemia also activates thrombosis and it is denoted by the American heart association that glucose >140 mg/dL.[16] Transitory hyperglycemia and glycosuria are common even in non diabetics during acute AMI. However, studies have shown that such patients are actually latent diabetics.[17] Hyperglycemia / diabetes increase the risk of cardiovascular events due to insulin resistance, changes in endothelial function, dyslipidemia, chronic inflammation and release of mediators of inflammation, procoagulability, impaired fibrinolysis all of which lead to the increased production of reactive oxygen species (ROS).[18]

Serum creatinine is slightly increased in ischemia and infarction in comparison to control group. Studies reported they do not have any significant role in the diagnosis of CAD.[19] In the current study, there is an evidence of increased serum value of lipids in chronic stable IHD. Dyslipidemia is one of the major risk factors for atherosclerosis. The lipid profile in AMI showed increased levels in comparison to the control group. HDL is one of the major carriers of the cholesterol in the blood from extra hepatic tissues to liver (excretion in to bile) i.e. reverse cholesterol transport. The additional functions of HDL include anti-inflammatory and antioxidant activity. HDL reduces the oxidized lipid particles in LDL and makes them less atherogenic.[20] Decreased levels of HDL is generally

due to hyper triglycereidemia or interference by paraproteinemia or from monogenic disorders like Tangiers disease, LCAT deficiency and apo A-I deficiency. Low HDL increases the risk of CAD. The oxidised LDL has got sticky nature and infiltrates into the intimal region of arterial wall and taken up by macrophages to cause foam cell formation. This is followed by atherosclerosis.[21] It was reported that during post AMI, the raised levels of TAG in serum is due to increased cellular uptake of cholesterol for hormonal synthesis and tissue repair.[22] The present work is in agreement with the findings of Ferdous et al[23] that total cholesterol, TAG and LDL cholesterol significantly increased and HDL cholesterol was significantly lower in serum of IHD cases when compared with control. Growing evidence revealed that atherosclerosis is an inflammatory process initiated by vascular injury, oxidized LDL, ROS, DM and infections. Some studies reported that there was neither decrease in HDL nor increases in LDL in patients with AMI.[24] The present study observed HDL is decreased (an atheroprotective) in ischemic cases when compared to control. Studies reported the serum values of lipids are increased in chronic stable IHD but there is no change in HDL when compared to control group.[25] The raised levels of serum TAG, LDL, VLDL and total cholesterol in ischemic cases as well as infarction cases in comparison to control, can be attributed to risk of CAD. Increased fasting TAG is associated with increased cardiac risk because of the elevated production of atherogenic residual lipoproteins. People may develop premature CAD due to genetic predisposition.[26]

LFT did not show any significant change in ischemic group as compared to control in this study. Some studies observed slight rise in liver enzymes especially AST and ALT in IHD cases due to fatty infiltration in the liver cell associated with obesity (increased BMI).[27] The liver enzymes of LFT are increased in AMI and showed significant difference from those of control within 2 to 3 hours from the onset of symptoms. The present study does not support the results of Okuhara et al, 2010, that there is elevation of total bilirubin in AMI.[28] The serum levels of AST showed significant elevation and this elevation is common in STEMI due to leakage from myocardial damage. Also, there is a positive correlation between elevated transaminases and atherosclerosis.[29] Wannamethee et al, 2013 reported that ALP provides a better predictive value for MI. It was observed in the present study, there is wide variation of non-cardiac parameters in the AMI group is due to limited sample size and the samples of admission period were analaysed.[30] However, the sample size which is included in the current study is based on statistical studies

Conclusion

The elevation of the serum cardiac markers will occur only when there is a transient damage of tissue myocardium. The risk factors influence the setting of CAD right from foetal stage and the rise in the non cardiac markers will be associated with ischemia and infarction of heart either directly or indirectly. The major purpose was to evaluate the usefulness of non cardiac parameters in predisposing to myocardial ischemia (as risk factors). In comparison to AST, ALT and ALP, the regular monitor of FBS, total cholesterol, triglycerides, LDL and VLDL along with cardiac markers will helpful to understand the progression towards ischemia as these are the contributing factors.

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