



## A PROSPECTIVE STUDY OF THE IMPACT OF LOW HIGH-DENSITY LIPOPROTEIN-CHOLESTEROL LEVEL ON 2-YEAR CLINICAL OUTCOMES AFTER ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH DIABETES MELLITUS

### Medicine

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### ABSTRACT

A total of 200 AMI patients with diabetes mellitus at RIMS, RAIPUR were divided into two groups based on HDL-C level on admission: normal HDL-C group (HDL-C  $\geq$  40 mg/dL, n = 100) and low HDL-C group (HDL-C < 40 mg/dL, n = 100). The primary endpoint was 2-year major adverse cardiovascular events (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR). In patients with diabetes mellitus, low HDL-C remained an independent risk predictor for MACE after adjusting for multiple risk factors during 2-year follow-up of AMI. Our main findings of the present study are as follows: (1) 46.2% of diabetic patients presenting with AMI had a low HDL-C level; (2) 2-year clinical outcomes including MACE (mainly cardiac death and TVR) were poorer in diabetic patients with a low HDL-C level after AMI compared to those with a normal HDL-C level; (3) low HDL-C level remained an important risk predictor for MACE after adjusting for confounding clinical factors.

### KEYWORDS:

High-density lipoprotein cholesterol, Major adverse cardiovascular events, Acute myocardial infarction, Diabetes mellitus, Risk-factors

### INTRODUCTION:-

Acute myocardial infarction (AMI) is a leading cause of mortality in patients with diabetes mellitus. Recent data revealed a 10–15% 1-year mortality rate after AMI in a diabetic population. Preventive strategies targeting platelet activity and lipid profiles in addition to glycemic control and lifestyle modification are an essential part of management in these patients. Previous primary prevention trials revealed that low high-density lipoprotein cholesterol (HDL-C) level is a significant risk factor for cardiovascular events in the general population. The Treating to New Targets (TNT) study revealed that approximately 15% of patients with diabetes mellitus have low HDL-C level. In diabetes, insulin resistance increases triglyceride-enriched HDL particles and causes more rapid clearance of HDL particles. Thus, low HDL-C is more common in diabetic patients. Moreover, previous epidemiologic studies demonstrated a higher prevalence of low HDL-C in the Asian population. The association between low HDL-C and coronary heart disease seemed to be stronger in the Asian population compared to non-Asians. Recently, low HDL-C levels have been reportedly associated with a higher rate of cardiovascular events in patients with stable coronary artery disease, percutaneous coronary intervention, or even AMI. However, it is still controversial whether low HDL-C affects cardiovascular outcomes after AMI. In addition, no studies have evaluated AMI patients with diabetes mellitus. In the present study, we have investigated the prevalence of low HDL-C and its long-term clinical impact in diabetic patients after AMI.

### MATERIALS AND METHOD

This study was a done at RIMS, RAIPUR between April 2013 and December 2016, 200 diabetic patients admitted for AMI were enrolled. The study participants were encouraged to follow up at 1, 6, 12, and 24 months after discharge. Written informed consent was obtained from all patients. AMI was defined based on elevated cardiac troponin-I or T level (exceeding upper limit of normal) or creatine kinase-MB fraction (CK-MB) (exceeding three times upper limit of normal), along with angiographic evidence. Angiographic evidence for AMI included significant coronary stenosis, i.e., more than 50% luminal stenosis, intracoronary filling defect or haziness suggesting coronary thrombus/vulnerable plaque, or coronary artery vasospasm confirmed by intracoronary acetylcholine or ergonovine provocation test. Diabetes mellitus was defined by

fasting plasma glucose level on two separate occasions  $\geq$  126 mg/dL, a random plasma glucose level  $\geq$  200 mg/dL, 2-h plasma glucose post-75 g dextrose load on two separate occasions  $\geq$  200 mg/dL, or taking oral hypoglycemic agents or using insulin. Dyslipidemia was defined as total cholesterol level  $\geq$  240 mg/dL, low-density lipoprotein cholesterol (LDL-C) level  $\geq$  130 mg/dL, HDL-C level < 40 mg/dL, triglyceride level  $\geq$  150 mg/dL, and/or treatment with lipid lowering agents. Low HDL-C was defined as < 40 mg/dL. Renal function was estimated with the glomerular filtration rate (eGFR), which was calculated with the Modification of Diet in Renal Disease (MDRD) equation as following:  $eGFR (mL/min/1.73 m^2) = 175 \times (\text{serum creatinine level})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ . In the present analysis, major adverse cardiac events (MACE) was defined as a composite of cardiac death, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR). Revascularization other than TVR (non-TV) was also analyzed. Definite stent thrombosis was assessed according to the Academic Research Consortium definition. Categorical variables were reported as count (percentage) and continuous variables as the mean  $\pm$  standard deviation. Comparisons between two groups were performed using the independent Student's t-test for continuous variables, and the  $\chi^2$  test for categorical variables. Kaplan–Meier survival curves with a log-rank test and Cox proportional hazard model analyses were performed to compare the long-term incidence of MACE and cardiac death between the two groups. The univariate and multivariate Cox proportional hazard regression analyses were used to identify risk predictors for MACE and cardiac death. The risk factors were tested with the multivariate Cox proportional hazard regression model by the backward selection method. The candidate variables for the model included HDL-C level, age, men, body mass index (BMI), current smoking, previous MI, ST-segment elevation myocardial infarction (STEMI) on admission, primary percutaneous coronary intervention (PCI), hypertension, statin use, estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c) level, high-sensitivity C-reactive protein (hsCRP) level, LDL-C level, left ventricular ejection fraction (LVEF), multivessel disease, lesion type (B2/C), stent diameter  $\leq$  2.75 mm, and stent length  $\geq$  28 mm. The selection significance level was 0.1. The results were expressed as the hazard ratio (HR) with a 95% confidence interval (CI) and p-value. All tests were two-tailed, and p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using

SAS (v. 9.3, SAS Institute Inc., USA).

## RESULT

Among a total of 200 diabetic patients who experienced AMI, 47.3% were in the low HDL-C group. The low HDL-C group had more men ( $p = 0.002$ ). There were fewer patients with newly diagnosed diabetes mellitus in the low HDL-C group ( $p = 0.034$ ). Laboratory findings showed lower total cholesterol and higher triglyceride levels in the low HDL-C group ( $p < .001$ ). Angiographic findings showed no significant difference between the two groups. There were no significant differences in in-hospital deaths and complications between the two groups. The 2-year clinical outcomes were assessed in the remaining 200 patients after excluding the patients with in-hospital death. Median follow-up period was 730 days. During the follow-up period, the incidence of MACE, cardiac death, and TVR was significantly higher in the low HDL-C group (MACE, 7.44% vs. 3.49%,  $p = 0.006$ ; cardiac death, 3.72% vs. 0.97%,  $p = 0.004$ ; non-fatal MI, 1.75% vs. 1.55%,  $p = 0.806$ ; TVR, 3.50% vs. 0.97%,  $p = 0.007$ ). Kaplan-Meier analysis revealed that the low HDL-C group had a significantly higher incidence of MACE and cardiac death compared to the normal HDL-C group (MACE, log-rank  $p = 0.012$ ; cardiac death, log-rank  $p = 0.005$ ). In multivariable Cox proportional hazard model analyses, HDL-C level, BMI, hypertension, and eGFR were independent significant predictors for MACE [HDL-C, HR (95% CI) 0.95 (0.905 - 0.999),  $p = 0.047$ ; BMI, HR (95% CI) 0.84 (0.714 - 0.993),  $p = 0.041$ ; hypertension, HR (95% CI) 4.80 (1.052 - 21.927),  $p = 0.043$ ; eGFR, HR (95% CI) 0.981 (0.966 - 0.996),  $p = 0.016$ ] after adjusting for conventional risk factors. LVEF remained the only independent predictor for cardiac death [HR (95% CI) 0.893 (0.828 - 0.964),  $p = 0.004$ ].

## DISCUSSION

Our main findings of the present study are as follows: (1) 46.2% of diabetic patients presenting with AMI had a low HDL-C level; (2) 2-year clinical outcomes including MACE (mainly cardiac death and TVR) were poorer in diabetic patients with a low HDL-C level after AMI compared to those with a normal HDL-C level; (3) low HDL-C level remained an important risk predictor for MACE after adjusting for confounding clinical factors. Previous community-based primary prevention studies showed that low HDL-cholesterol level was strongly associated with poor cardiovascular outcome in the general population. Current guidelines strongly recommend statin therapy for patients with overt atherosclerotic vascular diseases and diabetes mellitus. A previous study demonstrated that statin therapy increased HDL-C level by approximately 7.5%, and was associated with coronary atherosclerotic regression. However, more than 40% of statin-treated patients have a persistently low HDL-C level. Several studies also suggested low HDL-C as an independent risk predictor, even in patients with overt atherosclerotic vascular diseases on statin therapy. Seo et al. reported that a low HDL-C level on statin therapy was associated with poor clinical outcome after PCI. Ogital et al. also showed that low HDL-C was a risk factor in diabetic patients with stable coronary artery disease. Recently, Lee et al. showed similar results in patients with AMI. The present study showed a higher MACE rate in diabetic AMI patients with low HDL-C level compared to those with a normal HDL-C level. On the other hand, several studies have questioned the impact of HDL-C on cardiovascular prognosis. Izuohara et al. showed that the statistical significance of low HDL-C in poor clinical outcomes disappeared after adjusting for confounding factors in patients who underwent PCI. Angeloni et al. showed similar 3-year MACE rates in low and high HDL-C groups, even in patients who underwent coronary artery bypass grafting. Ji et al. also showed no significant difference in 1-year MACE rates between the two groups in AMI patients. Interestingly, the studies using the cut-off value of 40 mg/dL suggested that low HDL-C was an independent risk predictor. Other studies using different cut-off values for men and women (40 mg/dL for men and 50 mg/dL for women) failed to show the significance of low HDL-C. More importantly, 2 studies from the same AMI registry showed different results. One adopted the cut-off value of 40 mg/dL for both men and women, and the other study used different cut-off

values for men and women (40 mg/dL for men and 50 mg/dL for women). In the present study, receiver operating characteristic (ROC) curves of HDL-C for cardiac death showed that the area under the curve (AUC) for men was 0.722 and 0.753 for women (Additional file: Figure S1); optimal cut-off points with the Youden index were 38 mg/dL for men and 35 mg/dL for women. ROC curves of HDL-C for MACE showed that the AUC for men was 0.634 and 0.660 for women; optimal cut-off points with the Youden index were 38 mg/dL for men and 40 mg/dL for women. Thus, we used the same cut-off value of 40 mg/dL for both men and women. A genetic mechanism reportedly links low HDL-C and inflammatory states. Hoven et al. also showed a clinical relationship between low HDL-C level and its inflammatory and oxidative phenotype. Moreover, there is much experimental evidence for the beneficial effects of HDL-C. Although previous clinical trials aimed at raising HDL-C failed to show promising results, new HDL-C-based strategies designed to improve HDL-C functionality instead of increasing the HDL-C level have been under development. There are several limitations. First, the study subjects were divided into only 2 groups. We did not address the impact of the other ranges of HDL-C level (e.g., HDL-C > 70 mg/dL or < 20 mg/dL) due to the limited patient numbers. Thus, the possible protective role of high HDL-C level or its dose-response relationship could not be investigated. Second, the current guidelines recommend statin therapy for diabetic patients regardless of their lipid profile. Detailed information (name and dose) on statins and other medications affecting HDL-C levels were not assessed. However, the effect of statins on HDL-C has been known to be relatively small. Moreover, our data highlighted the clinical limitations of current statin usage and proposed HDL-C as a therapeutic target despite the failures of previous trials. Third, the follow-up rate of HDL-C was only 62.0% in the present study. Data on HDL-C levels before admission were not obtained. Thus, we cannot analyze the dynamics of HDL-C. Fourth, serum uric acid level was not included and adjusted for a potential confounding factor. Although the relationship between serum uric acid level and the prognosis of acute myocardial infarction has been still controversial, serum uric acid level is a well-known surrogate marker for inflammation and atherosclerosis. Unfortunately, serum uric acid level was not available in our registry. Additional data including serum uric acid level and other inflammatory biomarkers could be more informative to understanding the clinical impact of HDL-C.

## CONCLUSION

The 2-year incidence of MACE, cardiac death, and TVR was significantly higher in diabetic patients with a low HDL-C level compared to those with a normal HDL-C level after AMI. Low HDL-C level remained an independent risk predictor for both MACE and cardiac death after adjusting for multiple risk factors.

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