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Review Article

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Adipose Triglyceride Lipase Single Nucleotide Polymorphism is Associated with Heart Failure Development after Acute Myocardial Infarction in Patients with Dyslipidemia

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Abstract

Introduction: *There is limited information on the incidence of diabetes despite INDIA being the Global capital for Diabetes. Though much of data is available in patients already diagnosed with diabetes but data regarding the new onset diabetes in the subset of Acute coronary syndrome (ACS) is very limited.*

Materials and methods: *This was a Cohort study in which 200 consecutive ACS patients were included. Lab data about their FBS; PPBS; Lipid profile & Hba1c, BMI , BP and their clinical status was collected at the time of admission, after discharge at 2 weeks, 6 weeks & 3,6 & 12 months post ACS.*

Results: *In study 85% were males. Mean age was 56 years. Prevalence of various atherosclerotic risk factors in study population matched the regional prevalence of them.*

20% (n=40) developed New onset diabetes (NOD), 2.5% (n=5) developed Impaired fasting Glucose, 6% (n=12) developed Impaired glucose tolerance in and 1.5% (n=3) developed both Impaired fasting glucose and Impaired Glucose tolerance over a follow up period of 1 year. MACE rates & Revascularisation rates were significantly higher in NOD population. NOD patients had significantly higher BMI, waist circumference, BP, TG, LDL and Low HDL. NOD patients were on Higher dosage of statins, diuretics and Beta blockers.

Conclusion: *The study highlights two important things, first incidence of new onset diabetes in acute coronary syndrome patients is High, Second new onset diabetes has a significant impact on the clinical outcome of ACS patients*

Keywords: Acute Coronary Syndrome, New Onset Diabetes, Incidence

Introduction

Several studies suggested that cardiac steatosis may lead to diastolic cardiac dysfunction in patients with type 2 diabetes mellites [1-2]. Adipose triglyceride lipase (ATGL), also known as patatin-like phospholipase domain containing 2 (PNPLA2), is a crucial enzyme in the lipolysis cascade which catalyzes the rate-limiting step of lipolysis, i.e. the breakdown of triacylglycerol to diacylglycerol [3-5]. We have recently reported cases of ATGL genetic deficiency with a massive triglyceride deposit in cardiovascular systems, causing in cardio-myovasculopathy and severe heart failure [6-8]. These lines of evidence suggest that functional variants in the ATGL gene may cause lipid accumulation in cardiomyocytes and cardiac dysfunction. In this study, we thus evaluated the impact of ATGL single nucleotide polymorphism (SNP) genetic variant on heart failure hospitalization in patients after acute myocardial infarction (AMI).

Rs7925131 is one of the SNPs in the ATGL gene, which was associated with plasma triglyceride levels in European ancestry individuals [9]. We thus genotyped rs7925131 polymorphism in 4056 patients with acute myocardial infarction (AMI) who were registered to Osaka Acute Coronary Insufficiency Study (OACIS) between 1998 to 2010 and gave a written informed consent to the genotyping study. The OACIS is a multicenter, prospective, observational registry for AMI in Japan and is registered to the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) in Japan (ID: UMIN000004575) [10-13]. The primary end-point was set as 5-year heart failure hospitalization rate after survival discharge of AMI. Event rates were estimated using Kaplan-Meier analysis and compared using log-rank test. The impact of rs7825131 homozygous carriers (TT) on primary end-point was evaluated as hazard ratio (HR) and its 95% confidence interval (CI) using multivariable Cox regression analysis adjusted with patient demographics and medications at discharge. Statistical significance was set as $p<0.05$. All statistical analyses were performed using

R software packages version 3.1.0 (R Development Core Team).

Among the patients enrolled in the present study, median age was 65 (quartile 57-73) years old, 77.4% were male, 46.9% had a history of dyslipidemia and 90.7 % underwent percutaneous coronary intervention for AMI. The proportions of CC, CT and TT carriers were 43.1%, 45.7%, and 11.2%, respectively. Kaplan-Meier analysis revealed that patients with rs7825131 TT had higher incidence of heart failure hospitalization in patients with dyslipidemia after survival discharge of AMI, while not in those without dyslipidemia (p for interaction=0.045) (Figure). Multivariable Cox regression analysis demonstrated that rs7825131 TT genotype was associated with higher incidence of heart failure hospitalization after AMI in patients with dyslipidemia after adjustment for patient demographics and medications at discharge (HR 2.51, 95% CI 1.38-4.55, p=0.003), but was not in those without dyslipidemia.

In this study, we demonstrated that ATGL rs7825131 homozygous carriers with dyslipidemia had higher incidence of heart failure hospitalization after discharge of AMI. Although this ATGL variant was reported to be associated with impaired lipid metabolism, this is the first report that functional variant of the ATGL gene was associated with cardiovascular phenotype in relation with dyslipidemia [9]. Accumulation of triglycerides or other lipids in myocardium is a possible explanation for this observation, since it has been reported that intrinsic abnormalities of cardio-myocyte lipid metabolism can lead to cardiac dysfunction, despite a lack of clear evidence identifying association between ATGL rs7825131 genetic variant and intrinsic cardio-myocyte lipid metabolism in the present study. Along with the industrialization and civilization of the society, it has been reported that the number of patients with ischemic HF is increasing worldwide [1-2,7-9,14-18]. Thus, primary and secondary prevention of ischemic HF is now an emerging agenda in the contemporary clinical settings. However, the mechanism of HF progression after AMI has not been fully understood so far [13-16]. Thus, we hope our findings may give physicians a new insight to prevent ischemic HF, since the present results clearly demonstrated an association between ATGL genetic variant and HF development in the secondary prevention of AMI. Therefore, it should be urgently addressed whether management of serum and/or cellular lipid metabolism could prevent HF development in rs7925131 homozygous carriers after AMI.

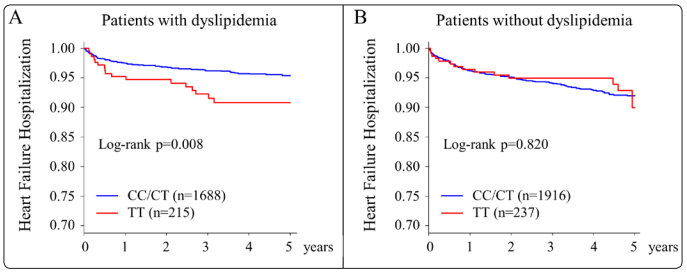

Figure: Kaplan-Meier curves

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