

## ABSTRACT

Myocardial Infarction (MI) is one of the major cardiovascular diseases worldwide. It is caused by rupture of atherosclerotic plaque in coronary vessels. Genetic and environmental factors play a key role in the development of MI. The major objective of current study was to evaluate the association of genetic variants with lipid metabolism and predisposition risk factors along with environmental factors in MI patients of Pakistani population. The study was designed in two phases; the first phase included demographic characteristics and economic burden of MI while the association of genetics with MI was investigated in the second phase. A total of 515 patients of MI were recruited to identify the economic burden, life style, family history and risk factors (hypertension, diabetes, smoking and hyperlipidemia) with MI. In second phase 384 Pakistani individuals were included for genetic analysis. A total of nine candidate genes with 22 SNPs were selected and genotyped by sequencing as well as one label extension method. The MI was significantly higher ( $P < 0.05$ ) among males as compared to females in both urban and rural MI patients. The 43.11% patients were overweight (BMI > 25). The urban MI patients were significantly more overweight as compared to rural patients ( $P < 0.05$ ). The 72.04% patients were found with previous family history of heart attack. Smoking (60.9%) and sedentary life style (70%) were more common in MI patients. Sedentary life style was predominant in Urban MI patients as compared to rural MI patients. The average annual cost per patient was found 9524.53 PKRs (96.96 USD). In genetic analysis 15 SNPs (out of 22) from 9 candidate genes were significantly ( $P < 0.05$ ) associated with elevated risk of MI. Overall current study was the first to identify three novel SNPs rs10757278, rs10811656 and rs10757283 on chromosome 9p21.3 (*CDKN2A/B* gene) using 11 genetic markers, against MI in Pakistani population. The genetic variants rs10811656 risk allele T and rs10757278 risk allele G, rs10757283 risk allele T residing at chromosome 9p21.3 were found to be significantly associated with higher risk of MI [OR = 1.67 (1.22, 2.29), 1.37 (1.09, 1.72) and 1.47 (1.08, 2.01) respectively]. Two lipid metabolism related SNPs: rs662799 and rs3135506 of *APOA5*

were associated with risk of higher triglyceride levels (266 mg/dl genotype GG and 244 mg/dl genotype CC respectively) irrespective of age, gender, obesity, diabetes, hypertension and smoking. Four SNPs (rs2383206, rs2383207, rs10811656 and rs10757278) of *CDKN2A/B* (chromosome 9p21.3) were found in strong linkage disequilibrium [LD ( $D' = 0.99$ )] and their minor allele frequencies were significantly more prevalent in patients than controls ( $P = 0.02, 0.0002, 0.0012, 0.005$  respectively). The four SNPs from 9p21.3 showed one risk haplotype (G-A-T-G;  $P = 0.001$ ) and two protective haplotypes (A-G-C-A and G-G-C-A;  $P = 0.006, 0.001$  respectively) involved in progression of MI. In addition the SNPs rs3135506, rs1558861, rs662799 and rs10750097 residing in *APOA5* gene were depicted strong linkage disequilibrium ( $D' = 0.99$ ). Present study identified C-T-G-A and G-C-A-G haplotypes as risk haplotypes significantly ( $P = 0.0001$ ) associated with MI. Higher BMI, smoking, hypertension, hyperlipidemia and diabetes were identified as strong predictor of MI in North Punjab Pakistan. Current study confirms correlation between lipid metabolism related SNPs and variants of 9p21.3 locus with MI as well as supporting the role of *APOA5* in raising the triglyceride levels. Preventive measures are needed to start at early age and continue throughout the life course. However further studies are needed for delineating the role of these SNPs in MI development.