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STATUS OF OXIDATIVE STRESS AND CHARACTERIZATION OF *APOB* GENE MUTATION IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA

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MSc

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic disorder characterized by high cholesterol concentration which increases oxidative stress and leads to coronary artery disease. Mutation in exon 26 and exon 29 of Apolipoprotein B (*APOB*) gene is one of the causes of FH. Oxidized low-density lipoprotein (ox-LDL), F_2-isoprostanes (ISP) and Malondialdehyde (MDA) are established oxidative stress biomarker. The aim of this study is to investigate oxidative stress status and to identify genetic variants in *APOB* gene among FH patients and normocholesterolaemic (NC) subjects. Ninety-eight FH patients and 100 (age, gender and BMI matched) NC subjects were recruited in series of health screening programmes across the country. Fasting blood samples were analysed for serum ox-LDL (ELISA), ISP (LCMS/MS) and MDA. Amplicons of exon 26 and 29 of *APOB* gene were screened by DNA sequencing. Ox-LDL, ISP and MDA concentrations were significantly higher in FH groups compared to NC (mean$\pm$SEM: 63.0$\pm$6.5 vs 25.5$\pm$1.2 (U/l), $p<0.001$); 749.7$\pm$74.0 vs 354.2$\pm$18.1 pg/ml, $p<0.0001$; 342.4$\pm$46.0 vs 162.7$\pm$13.5 nmol/g, $p<0.0001$). Ox-LDL shows significant correlation with glucose ($p<0.05$), TC ($p<0.001$), LDL-c ($p<0.001$) and HDL-c ($p<0.01$) in all subjects. High LDL-c was associated with high ox-LDL ($p<0.001$). LDL-c is an independent predictor for ox-LDL concentration ($p<0.001$). Known mutations were not found in all FH cases except for few insignificant genetic variations which are pThr2515Thr, p.Ile2716Ile, p.Pro2739Leu, p.Glu4181Lys, p.Arg4270Thr, p.Arg4297His and p.Ser4338Asn. These findings demonstrate that FH patients have higher oxidative stress concentration which suggests a greater risk of developing atherosclerosis. These results provide additional knowledge regarding FH in Malaysians.

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Read in the name of your Lord Who created. He created man from a clot. Read and your Lord is Most Honorable, Who taught (to write) with the pen. Taught man what he knew not. (Surah Al Alaq 96:1-5)

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