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SOLUBLE INFLAMMATORY BIOMARKERS AND APOLIPOPROTEIN A1 GENE VARIANTS IN LOW HIGH DENSITY LIPOPROTEIN CONCENTRATION

NURUL ATIQAH BINTI MOHD MOKHSIN

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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.

Name of Student	:	Nurul Atiqah Binti Mohd Mokhsin
Student I.D. No.	:	2010730297
Programme	:	Master of Science (Medicine)
Faculty	:	Medicine
Thesis Title	:	Soluble Inflammatory Biomarkers and Apolipoprotein A1 Gene Variants in Low High Density Lipoprotein Concentration
Signature of Student	:	.....
Date	:	June 2016

ABSTRACT

Atherosclerosis leads to coronary artery disease (CAD) is a main cause of death worldwide. Low High density lipoprotein (HDL-c) concentration has been associated with increased inflammation, which causes increase risk of CAD. Nevertheless, inflammatory status of low HDL-c subjects and primary causes due to variations of the apolipoproteinA1 (*APOA1*) gene involved in HDL-c metabolism have not been extensively studied. Hence, this study compared serum concentration of inflammatory biomarkers [interleukin (IL)-6 and high sensitivity c-reactive protein (hsCRP)] between low HDL-c subjects and matched controls, studied the association between HDL-c and inflammatory biomarkers concentrations, determined if HDL-c is an independent predictor of inflammatory biomarkers, and identified variations of the *APOA1* gene in low HDL-c subjects compared with matched controls. This study consisted of two parts; biochemical and genetic association studies. Two hundred and seven (207) low HDL-c subjects and 215 matched controls were recruited in the biochemical study, while 70 low HDL-c subjects and 140 matched controls were included in the genetic association study. Serum and whole blood samples were collected for analysis of biochemical and genetic association studies respectively. The results showed enhanced inflammatory biomarkers in low HDL-c subjects, and inverse association was discovered between HDL-c and inflammatory biomarkers, as well as HDL-c was an independent predictor for IL-6. Furthermore, four variants of *APOA1* gene were significantly associated with low HDL-c concentration. In conclusion, low HDL-c concentration is strongly correlated to the enhanced inflammatory biomarkers, whereas *APOA1* gene may play an important role in low HDL-c subjects in this study.

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CHAPTER ONE
INTRODUCTION

1.1 RESEARCH BACKGROUND

Atherosclerosis is defined as presence of focal thickening atherosclerotic plaque (atheroma) of the innermost layer; tunica intima and middle sized elastic muscular arteries (Yutaka Nakashima, Fujii, Sumiyoshi, Wight, & Sueishi, 2007). The atheroma within the tunica intima consists of a lipid core and a covering fibrous cap (Libby, 2002). The lipid plaque is composed of cholesterol and cholesterol esters, either contained within foam cells of macrophage origin or as products of extracellular matrix (Badimon, Martínez-González, Llorente-Cortés, Rodríguez, & Padró, 2006). The extracellular matrix is made up of smooth muscle cells, collagen, elastic fibers and proteoglycans, surrounded by macrophages and other leukocytes. Atherosclerosis begins with damage to the endothelial wall caused by elevated cholesterol, systemic hypertension, and smoking, which lead to endothelial dysfunction (Hadi, Carr, & Al Suwaidi, 2005; Sitia et al., 2010). It is a major cause of coronary artery disease (CAD) (Hansson, 2005), cerebrovascular accident (CVA) (Kronzon & Tunick, 2006), and peripheral vascular disease (PVD) (Mascarenhas, Albayati, Shearman, & Jude, 2014). In 2009, CAD became the number one killer not only in Malaysia, but also worldwide (Planning Division Health Informatics Centre, 2014; World Health Organization, n.d.).

In many ways, atherosclerosis is a chronic inflammatory disorder and this is confirmed by previous investigations that have focused on the inflammatory state of atherosclerosis, providing new insight into mechanisms of disease (Libby, Ridker, & Hansson, 2011). The continuous immigration and infiltration of activated macrophages and T cells into and within atherosclerotic lesions are prominent features in both human and experimental atherosclerotic disease (Zernecke, Shagdarsuren, & Weber, 2008). The recruitment of these cells to lesions is guided by endothelial leukocyte adhesion molecules and chemoattractants (Charo & Taubman, 2004). In keeping with this formulation, the atherosclerotic plaque has, as its major components, macrophages, cells of the adaptive immune system, smooth muscle cells, and matrix