CHAPTER I

INTRODUCTION

I.1 Background

Low HDL-C level (less than 40 mg/dl) is the most common lipoprotein abnormality found in coronary artery disease (CAD) patients.[1] The risk of CAD is inversely correlated to the level of high-density lipoprotein cholesterol (HDL-C) in both women and men after regulating other lipid risk factors such as LDL cholesterol and triglycerides.[2] Identifying substantial genetic causes of low HDL-C and assigning its frequency in the population are important for understanding the common risk of low HDL-C in humans and improve the direct investigation ofthe correlation between HDL-C and CAD.[3]

The different prevalence of low HDL-C level can be found in several countries.[4] In Korea, the prevalence of low HDL-C level in their population is about 23.8% for men and 47.5% for women.[5] Low HDL-C level can be found in approximately 25% of men in UK.[6] A study at the Cipto Mangunkusumo Hospital, Jakarta Indonesia showed that low HDL-C level was found atherogenic.[7] The prevalence of low HDL-C level in Indonesia is about 43.6% for men and 57.8% for women.[4]

The causes of low HDL level can be monogenic, polygenic, environmental factor, or can be mixed relation between genetic and environmental factor.[3] Secondary causes affecting HDL-C level has been showed in some

epidemiological studies. The secondary causes include gender, age, obesity, smoking, alcohol consumption, diet, physical activity, medications (such as steroids), and metabolic disorders (for example insulin resistance and hepatic disease).[8,9]

The low HDL-C level with monogenic cause is rarely found and only elucidates the cause of the level of low HDL-C in general population less than 1%.[10] Subject with low HDL-C level may have correlation with hereditary. The prevalence of familial low HDL-C level is about 40-60% which is found in family studies and twin studies.[3] Several gene mutations are suspected to be the cause of low HDL-C level which posses to be the crucial part in HDL metabolism,[11] such as the mutation in *ABCA1* gene.[3]

ABCA1 gene encodes adenosine triphosphate-cassette binding transporter subfamily A member 1 which is located at chromosome 9q31.1. The *ABCA1* gene has a 149 kb length and contains 50 exons. *ABCA1* gene works as a cholesterol efflux pump in the celluler lipid removal pathway.[11] Mutation in this gene leads to decrease of HDL cholesterol level.[12] An autosomal recessive disorder known as Tangier disease is a familial alphalipoprotein deficiency characterized by absence of HDL-C caused by mutation in *ABCA1* gene.[3] Tangier patients have a 3 to 6 times the increased risk of premature CAD. The breakage of cholesterol efflux from macrophages induce the presence of foam cells throughout the body, which may explain an increasing the CAD risk in some Tangier disease families. *ABCA1*gene mutation heterozygosity results in about half-normal levels of HDL-C plasma.[13] Wang *et al*. reported, *ABCA1* is a very attractive candidate gene for

determination of plasma HDL-C level in the general population due to the impairment of cellular cholesterol efflux appeared to be abnormal in some patients FHA because there was mutation in *ABCA1*, but no obvious tissue deposition of cholesterol esters was presented and the reduction of HDL-C concentration was demonstrated an apparent autosomal codominant pattern of expression in *ABCA1* mutation carriers.[14]

The molecular technique high-resolution melting (HRM) is rapid, sensitive and cost effective to screen the mutation by differentiating the melting point in curve analysis.[15] Since the identification in *ABCA1* gene using HRM analysis has never been reported in Indonesian population, it will be beneficial to provide information about mutational screening for individuals with low-HDL level. Furthermore, correlation between *ABCA1* mutation and HDL-C level may has an important role for clinical management of patients with low level of HDL-C.

I.2 Research Question

I.2.1 General Research Question

Is there any predicted pathogenic mutation in *ABCA1* gene in subject with low level of high density lipoprotein?

I.2.2 Specific Research Question

1. Is there any variant of *ABCA1* gene in subject with low level of high density lipoprotein?
2. What is the distribution of variant alleles *ABCA1* gene in subject with low level of high density lipoprotein?
3. Is the identified variant *ABCA1* gene predicted to be pathogenic?
4. Is there any difference of HDL-C level between the group with and without risk factors of low HDL-C?
5. Is there any difference of HDL-C level in each genotype?

I.3. Research Purposes

I.3.1 General Purposes

To identify predicted pathogenic mutation of *ABCA1* genes in subject with low level of high density lipoprotein.

I.3.2 Specific Purposes

1. To identify variant of *ABCA1* genes in subject with low level of high density lipoprotein.
2. To analyze what is the distribution of variant alleles *ABCA1* gene in subject with low level of high density lipoprotein.
3. To analyze whether the identified variant gene is predicted to be pathogenic.

4. To identify the differences of HDL-C level between the group with and without risk factors of low HDL-C.
5. To identify differences of HDL-C level in each genotype.

I.4 Research Benefit

The benefit of this study is to provide information about mutation of *ABCA1* gene in subjects with low level of HDL-C which may important for clinical management of the patients with low level of high density lipoprotein.

1.5 Originality

This is a study to identify *ABCA1* gene mutation in Indonesian subjects with low HDL-C level. Table 1 shows the previous studies about identification of mutation in *ABCA1* gene.

Table 1. List of previous studies about identification of *ABCA1* gene mutation

No	Author	Title of Publication	Method	Result
1.	Knut Erik Berge, Trond .P.Leren (2010,Clinica Chimica Acta)[14]	Mutation in *APOA1* and *ABCA1* in Norwegian with low levels of HDL cholesterol.	Patients with a mean low HDL-C were subjected to DNA sequencing	Mutations in the genes that encode *ABCA1* and *APOA-I* are the most common causes of hypoalphalipoprotei nemia in Norwegians.
2.	Hu S, Zhong Y, Hao Y, Luo M, Zhou Y, Guo H, Liao W, Wan D, Wei H, Gao Y, Shan J, HuB, Hultén M,WangY. (2009, Clinical Chemistry Laboratory Medicine) [16]	Novel rare alleles of ABCA1 are exclusively associated with extreme high-density lipoprotein-cholesterol levels among the Han Chinese.	Samples were collected for 470 subjects, Extreme groups of low and normal HDL-C were sequenced, then genotyped the non-synonymous variants identified exclusively with either extreme group.	Four novel non-synonymous alleles were identified; all were rare. Alleles c.3029C>T (p.Ala1010Val) and c.5399A>G (p.Asn1800Ser) were found exclusively in the low group, c.2031C>A (p.Asp677Glu) and c.2660G>T (p.Cys887Phe) exclusively in the high group.