UNIVERSITI PUTRA MALAYSIA

CREATINE KINASE AND SLCO1B1 RS4363657 POLYMORPHISM IN MALAYSIAN DYSLIPIDAEMIC PATIENTS PRESCRIBED WITH STATIN DRUGS

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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March 2016

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Faculty: Medicine and Health Sciences

Background: Statin, a first line treatment for dyslipidaemia has reduced patient compliance and is underprescribed because of its side effect of muscle toxicity. The incidence of statin-induced muscle toxicity ranges from 1% to 7%, whereas severe muscle toxicity occurs in up to 0.5% of patients. In Malaysia, however, this data remains limited, due to under-reported, mis/underdiagnosed cases or statin-induced muscle toxicity is generally rare.

Aim: The aim of this study is to analyse the association of serum creatine kinase (CK) and rs4363657 polymorphism of *SLCO1B1* gene with statin-induced muscle toxicity, and the lipid-lowering effects of different type of statins (simvastatin and lovastatin) prescribed among dyslipidaemia patients.

Methodology: This was a prospective cohort study involving 118 newly diagnosed adult patients with dyslipidaemia who were prescribed a statin for the first time. Statin-induced muscle toxicity was recorded based on the complaint of muscle aches and pains on follow-up after 1 month on statin. Biochemical analyses (CK, fasting lipid profile, apo A1, apo B) were done on the first and follow-up appointments. Genetic profiling was done for rs4363657 polymorphism of *SLCO1B1* gene. Data was analysed using IBM SPSS Statistics version 22.0 for Windows.

Results: The study showed significance difference in the effect of lovastatin and simvastatin on all lipid profile parameters (TC, HDL-C, LDL-C, LDL:HDL, non-HDL-C, TC:HDL, apo A1, apo B, apo B:apo A1) except for TG ($p<0.05$). By comparing median change in lipid values between first and follow up appointments, simvastatin

had a significantly greater effect than lovastatin. There was significant association between types of statin prescribed with statin-induced muscle toxicity ($p = 0.0327$); frequency of muscle aches and pains being higher with lovastatin compared to simvastatin (15.25% vs 3.39%). However, there was no significance relationship between CK level with statin-induced muscle toxicity ($p = 0.5637$). The rs4363657 polymorphism of SLCO1B1 gene was significantly associated with statin-induced muscle toxicity ($p<0.0001$). The frequency of statin-induced muscle toxicity was highest in CC genotype (100%) followed by TC genotype (42.31%) and TT (wild type) genotype (3.57%). Patients with TC genotype and CC genotype are 26.241 times and 357.964 times more likely to exhibit statin-induced muscle toxicity than patients with normal *SLCO1B1* gene, respectively ($p<0.0001$).

Conclusion: Simvastatin had a better effect compared to lovastatin in improving all lipid parameters, including predictors of CVD risks. However, muscle toxicity was more significant in patients prescribed with lovastatin compared to simvastatin. CK was shown to be not a significant biomarker to indicate muscle toxicity. It can be concluded that *SLCO1B1* gene is a good genetic marker for statin-induced muscle toxicity. The only significant risk factor for statin-induced muscle toxicity in this study was rs4363657 polymorphism of *SLCO1B1* gene.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

CREATINE KINASE DAN _SLCO1B1_ RS4363657 POLIMORFISMA DI DALAM PESAKIT DISLIPIDEMIA DI MALAYSIA YANG MENERIMA UBAT STATIN

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Latar belakang: Statin, merupakan rawatan baris pertama bagi dislipidemia. Bagaimanapun, beberapa pesakit mungkin mengalami kesan toksik ke atas otot akibat daripada penggunaan statin, jika ia menjadi teruk boleh menyebabkan pesakit berhenti daripada mengambil ubat ini. Insiden bagi kesan toksik ke atas otot akibat daripada penggunaan statin adalah dari 1% hingga 7%, manakala insiden bagi kesan toksik yang teruk ke atas otot boleh mencecah sehingga 0.5%. Bagaimanapun di Malaysia, data-data ini masih sangat terhad, sama ada disebabkan oleh kurangnya laporan, kurang / kesilapan dalam diagnosis, ataupun insiden kesan toksik ke atas otot akibat penggunaan statin ini adalah jarang sekali berlaku.

Tujuan: Tujuan kajian ini adalah untuk menganalisis hubungan serum creatine kinase (CK) dan juga hubungan rs4363657 polimorfisma bagi gen *SLCO1B1* dengan kesan toksik ke atas otot yang disebabkan oleh statin, dan kesan pengurangan lipid bagi jenis statin yang berbeza (simvastatin dan lovastatin) yang diberikan kepada pesakit yang mengalami dislipidemia.

Kaedah: Kajian ini adalah kajian kohort prospektif melibatkan 118 pesakit-pesakit yang baru disahkan mengalami dislipidemia dan diberikan statin buat kali pertama. Kesan toksik ke atas otot yang disebabkan oleh statin direkodkan berdasarkan kepada aduan sakit otot semasa rawatan susulan iaitu sebulan selepas mengambil statin. Analisis biokimia (CK, serum lipid, apo A1 dan apo B) dibuat pada pertemuan kali pertama dan rawatan susulan. Profil genetik dibuat untuk menganalisis rs4363657 polimorfisma bagi gen *SLCO1B1*. IBM SPSS Statistics versi 22.0 bagi Windows digunakan untuk menganalisis data.

Keputusan: Kajian ini menunjukkan perbezaan yang signifikan bagi kesan penggunaan lovastatin dan simvastatin terhadap kesemua parameter lipid (TC, HDL-C, LDL-C, LDL:HDL, non-HDL-C, TC:HDL, apo A1, apo B, apo B:apo A1) kecuali TG ($p<0.05$). Melalui perbandingan perubahan median tahap lipid di antara pertemuan kali pertama dengan rawatan susulan, simvastatin menunjukkan kesan yang lebih baik berbanding dengan lovastatin. Terdapat hubungan yang signifikan di antara jenis statin yang diberikan dengan insiden kesan toksik ke atas otot ($p = 0.0327$); frekuensi bagi kesan toksik ke atas otot yang disebabkan oleh lovastatin adalah lebih tinggi berbanding dengan simvastatin (15.25% vs 3.39%). Bagaimanapun, tahap CK tidak menunjukkan hubungan yang signifikan dengan kesan toksik ke atas otot yang disebabkan oleh statin ($p = 0.5637$). rs4363657 polimorfisma bagi gen *SLCO1B1* menunjukkan hubungan yang signifikan dengan kesan toksik ke atas otot yang disebabkan oleh statin ($p<0.0001$). Frekuensi bagi kesan toksik ke atas otot yang disebabkan oleh statin adalah paling tinggi dalam genotip CC (100%) disusuli dengan genotip TC (42.31%) dan TT (3.57%). Pesakit dengan genotip TC dan genotip CC adalah 26.241 dan 357.964 kali ganda untuk mengalami kesan toksik ke atas otot disebabkan oleh statin berbanding dengan pesakit yang mempunyai *SLCO1B1* gen yang normal.

Konklusi: Simvastatin mempunyai kesan yang lebih baik berbanding lovastatin ke atas semua parameter lipid, termasuk parameter yang digunakan untuk meramalkan risiko bagi penyakit kardiovaskular. Bagaimanapun, sakit otot adalah lebih signifikan bagi pesakit yang menggunakan lovastatin. CK bukanlah penanda biokimia yang signifikan untuk mengenalpasti kesan toksik ke atas otot. Sebagai konklusi, gen *SLCO1B1* merupakan penanda genetik yang baik bagi kesan toksik ke atas otot akibat daripada penggunaan statin. Untuk kajian ini, rs4363657 polimorfisma bagi gen *SLCO1B1* merupakan satu-satunya faktor bagi menjangkakan risiko kesan toksik ke atas otot akibat daripada penggunaan statin.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee are as follows:

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LIST OF ABBREVIATONS

4-AAP	4-Aminophenazone
ABC	ATP-binding cassette
ACC	American College of Cardiology
ADP	Adenosine Diphosphate
AHA	American Heart Association
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ApoA1	Apolipoprotein-A1
ApoB	Apolipoprotein-B
Apo B-48	Apolipoprotein B-48
Apo B-100	Apolipoprotein B-100
Apo C-II	Apolipoprotein C-II
Apo E	Apolipoprotein E
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
$AUC_{dn,wt}$	Dose-per-bodyweight normalized area under the concentration-time curve
BMI	Body Mass Index
BP	Base Pairs
BSA	Bovine Serum Albumin
$Cmax_{dn,wt}$	Dose-per-body weight normalized maximum observed concentration
CE	Cholesterol Esterase
CHD	Coronary Heart Disease
CHOD	Cholesterol Oxidase
CK	Creatine Kinase
CO_2	Carbon Dioxide
CO_3^-	Carbonate
CoQ10	Ubiquinone or Coenzyme 10
CRP	C Reactive Protein
CVD	Cardiovascular Disease
CYP 450	Cytochrome P450 gene family enzymes
DVT	Deep Vein Thrombosis
EMG	Electromyography
eNOS	Endothelial Nitric Oxide Synthase
FBS	Fasting Blood Sugar
FDA	United States Food and Drug Administration
FFA	Free Fatty Acid
FSL	Fasting Serum Lipid
G6P	Glucose-6-phosphate
G6PDH	Glucose-6-phosphate Dehydrogenase
GGT	γ-Glutamyltranferase
GK	Glycerol Kinase
GLDH	Glutamate Dehydrogenase
GPO	Glycerol-3-phosphate Oxidase
H^+	Proton
H_2O	Water
H_2O_2	Hydrogen Peroxide
HDL	High Density Lipoprotein

HDL-C	High Density Lipoprotein Cholesterol
HK	Hexokinase
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HSDA	Sodium-N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline
IDL	Immediate Density Lipoprotein
IFCC	International Federation of Chemical Chemistry and Laboratory Medicine
IL	Interleukin
J-LIT	Japanese Lipid Intervention Trial
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein Cholesterol
Leu	Leucine
LFA-1	Lymphocyte Function-Associated Antigen-1
LFT	Liver Function Test
LPL	Lipoprotein Lipase
MCP-1	Monocyte Chemotactic Protein-1
MDH	Malate Dehydrogenase
MEGA	Management of Elevated Cholesterol in the Primary Prevention of Adult Japanese
MHC II	Major Histocompatibility Complex Type II
MMPs	Matrix Metalloproteinases
NADH	Nicotinamide Adenine Dinucleotide
$NADP^+$	Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Reduced Nicotinamide Adenine Dinucleotide Phosphate
NCBI	National Center for Biotechnology Information
NCEP	National Cholesterol Education Program
NCS	Nerve Conduction Study
NH_4^+	Ammonium
NHLBI	National Heart, Lung and Blood Institute
NLA	National Lipid Association
NO	Nitric Oxide
O_2	Oxygen
OATP1B1	Organic anion transporting polypeptide 1B1
OATP-C	Organic anion transporting polypeptide C
P_i	Phosphate
PAD	Peripheral Artery Disease
PAI-1	Plasminogen Activator-1
PCr	Phosphocreatinine
PCR	Polymerase Chain Reaction
POD	Peroxidase
PP_i	Pyrophosphate
ROS	Reactive Oxygen Species
RP	Renal Profile
SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
SLC	Solute carrier family gene family transporters
SLCO1B1	Solute carrier organic anion transporter family member 1B1
SNP	Single Nucleotide Polymorphism

SREBP	Sterol regulatory element binding protein
STRENGTH	Statin Response Examined by Genetic Haplotype Markers
T2DM	Type 2 Diabetes Mellitus
TAE	Tris-Acetate-EDTA
TCA	Tricarboxylic acid cycle
TF	Tissue Factor
TG	Triglyceride
TIA	Transient Ischaemic Attack
TLR4	Toll-Like Receptor 4
TNFα	Tumor Necrosis Factor-α
t-PA	Tissue Plasminogen Activator
Trp	Tryptophan
TXA_2	Thromboxane A2
UDP	Uridine Diphosphate
UGT	UDP-glucoronosyltranferases gene family enzymes
U.S	United States of America
VLDL	Very Low Density Lipoprotein
VLDL-C	Very Low Density Lipoprotein Cholesterol
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

Dyslipidaemia is one of the major risk factors for cardiovascular disease (CVD), particularly coronary heart disease (CHD), with a high risk for morbidity and mortality in Malaysia. Secondary prevention plays the most significant role in the management of CHD. Statin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor is a class of drugs that is commonly used to prevent vascular occlusive events due to dyslipidaemia. It is used as a standard therapy for managing patients with CVD (Barber et al. 2010; Zhou & Liao, 2009). Currently, there are various types of statins prescribed worldwide. Atorvastatin (Lipitor and Torvast), simvastatin (Zocor and Lipex), lovastatin (Mevacor, Altocor and Altoprev), pitavastatin (Livalo and Pitava), rosuvastatin (Crestor), fluvastatin (Lescol) and pravastatin (Pravachol, Lipostat and Selektine) are the common types of statins found in the market. Each of these statins has a different effect on lipid profile. However, a number of adverse events have been reported in patients prescribed with this class of drugs, most commonly being muscle toxicity. Cerivastatin (Baycol and Lipobay) was withdrawn from the market in August 2001 due to the high risk of rhabdomyolysis. However, patients often have heterogeneous responses to statin. This suggests the possibility of interindividual variability in response to statin treatment. The statin-induced muscle toxicity rate also can be affected by types of statins consumed due to slight difference in the structure and mechanism of action of each statin (Gazzerro et al., 2012; Kajinami, Mabuchi, & Saito, 2000; Mück et al., 1997; Tse, Jaffe, & Troendle, 1992).

Statin-induced muscle toxicity is the most common side effect of statin consumption. The incidence of statin-induced muscle toxicity ranges from 1% to 7%, whereas severe muscle toxicity with more than 10-fold elevation of creatine kinase (CK) occurs in up to 0.5% of patients. Statin discontinuation rate due to adverse events is 1% to 5% (Oh, Ban, Miskie, Pollex, & Hegele, 2007). In Malaysia, however, this data remains limited, due to under-reported, mis/underdiagnosed cases or statin-induced muscle toxicity is generally rare.

Genetic polymorphisms and drug interactions are contributing factors to the side effects of various medications. Both of these can lead to the alteration of the pharmacokinetics and pharmacodynamics of statin and may give rise to statin-induced muscle toxicity. Hyporesponders or non-responders are likely to have adverse muscular events during follow-up. Various genes with genetics variants have been identified to be responsible for this side effect such as *SLCO1B1* gene, *COQ2* gene and *CYP2D6*, *CYP3A4* and *CYP3A5* genes from the Cytochrome P 450 enzyme system (Ghatak, Faheem, & Thompson, 2010; Oh, Ban, Miskie, Pollex, & Hegele, 2007; Peters, Klungel, Visseren, de Boer, & Maitland-van der Zee, 2009; Rossi & McLeod, 2009; Vladutiu, 2008). Concomitant administration of certain drugs such as calcium channel blockers (verapamil and diltiazem), macrolide or ketolide antibiotics (erythromycin and

clarithromycin), azole antifungals and fibrates (gemfibrozil) can also increase the risk of adverse events by altering statin pharmacokinetics and pharmacodynamics (Bellosta, Paoletti & Corsini, 2004; Gazzerro et al., 2012; Wang, Casciano, Clement & Johnson, 2001; Mousa, Brater, Sunblad & Hall, 2000; Azie, Brater, Becker, Jones, & Hall, 1998; Wagner, Suessmair & Pfister, 2009; Chatzizisis et al., 2010; Neuvonen, Niemi & Backman, 2006; Fujino et al., 2003; Prueksaritanont, 2002).

1.2 Problem Statement

Recent findings show that muscle toxicity has become the main concern in statin prescription (Oh, Ban, Miskie, Pollex, & Hegele, 2007; Fernandez, Spatz, Jablecki, & Phillips, 2011). Although the exact mechanism of statin-induced muscle toxicity is unknown, possible aetiologies include decreased sacrolemmal or sarcoplasmic reticular cholesterol, reduced production of ubiquinone or coenzyme Q10, decreased production of prenylated proteins, changes in fat metabolism, increased uptake of cholesterol or phytosterols, failure to replace damaged muscle protein via the ubiquitin pathway, disruption of calcium metabolism in the skeletal muscle and inhibition of selenoprotein synthesis (Oh, Ban, Miskie, Pollex, & Hegele, 2007; Fernandez, Spatz, Jablecki, & Phillips, 2011; Harper & Jacobson, 2007; Ghatak, Faheem, & Thompson, 2010; Vladutiu, 2008).

Although serum creatine kinase (CK) can be used as a marker of muscle toxicity, it is non-specific for muscle damage and varies in individuals with muscle toxicity (Valiyil & Christopher-Stine, 2010). It is primarily found in muscle cells including the heart (CK-MB), striated muscles (CK-MM) and the brain (CK-BB). Therefore, it cannot be used as an absolute marker of muscle damage in statin-induced muscle toxicity. Furthermore, it has been shown that muscle biopsies from asymptomatic individuals taking statins have revealed subclinical damage in muscle cells (Laaksonen et al. 2006; Valiyil & Christopher-Stine, 2010). Being an invasive procedure, muscle biopsy is not a practical way of assessing statin-induced muscle toxicity. Thus, identification of genetics variants in these patients plays a paramount role in improving the safety and efficacy of statin use.

1.3 Significance of This Study

This study will provide genetic baseline data which may later indicate the best suitable statin treatment and dosage for Malaysian dyslipidaemia patients. Gene expression analysis proposed in this project aims to verify the association between proposed candidate genes with statin-induced muscle toxicity and lipid-lowering response to different statins before performing gene polymorphism and genotyping. With the final aim of developing a rapid DNA diagnostic test kit that will enable us to determine type of statin and dosage tailor suit for Malaysian dyslipidaemia patients according to their genetic backgrounds, it is hoped to improve management of dyslipidaemia in Malaysia, reduce patient's risk towards acute and chronic complications, which in turn will help reduce government health care cost. At the same time, this research hopes to fulfill the quest for personalised medicine in Malaysian dyslipidaemia population.

The basis of personalised medicine emphasises the role of genetics in dosing of specific drugs. Genetic variants exist in genes encoding enzymes and the variants alter individual responses to the drug consequently influencing the dosage requirement, Thus, clinicians should be made aware of these genetic variants in patients with statin intolerance so that genetic predisposition testing will become an integral component of personalised medicine that will contribute to the safe and informed use of selected drugs and improved compliance.

1.4 Objectives

The objectives of this study can be divided into general and specific objectives.

1.4.1 General Objective

The general objective of this study is to determine the biochemical and genetic markers associated with lipid-lowering effects of statins and statin-induced muscle toxicity in dyslipidaemic patients in Klinik Kesihatan Dengkil, Klinik Kesihatan Bandar Baru Bangi and Klinik Kesihatan Kajang in Malaysia.

1.4.2 Specific Objectives

The specific objectives of this study are to determine:

i. the effects of types of statins prescribed on non-conventional lipid parameter namely LDL:HDL ratio, non-HDL-C, TC:HDL ratio, apo A1, apo B, and apo B:apo A1 ratio;
ii. the relationship of types of statins and statin-induced muscle toxicity;
iii. the association of serum CK levels with symptoms of statin-induced muscle toxicity;
iv. the association of rs4363657 polymorphism of *SLCO1B1* gene in patients with statin-induced muscle toxicity.

1.5 Hypotheses

There are four (4) hypotheses for this study which include:

i. Different types of statins have differing effects on patients' LDL:HDL ratio, non-HDL-C, TC:HDL ratio, apo A1, apo B, and apo B:apo A1 ratio.
ii. Types of statins are significantly associated with events of statin-induced muscle toxicity.
iii. Statin-induced muscle toxicity is significantly associated with increased serum CK levels.
iv. Statin-induced muscle toxicity is significantly associated with rs4363657 polymorphism of *SLCO1B1* gene.

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