



UNIVERSITI PUTRA MALAYSIA

***PLATELET-RELATED BIOMARKERS AND LEPTIN LEVELS
IN OVERWEIGHT AND OBESE MALAYSIANS
IN A PUBLIC UNIVERSITY***

NASRIN RIYAH

FPSK(m) 2015 43



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By

NASRIN RIYAH



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

September 2015

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DEDICATION

I am sincerely delighted to dedicate this thesis to my husband, Sina Moghadas Khorasani, who has been a constant source of love, support and encouragement during the challenges of graduation and life. I am truly thankful for having you in my life.

This thesis is also dedicated to my father, who taught me that the best kind of knowledge to have is that which is learned for its own sake. It is also dedicated to my mother, who taught me that even the largest task can be accomplished if it is done one step at a time.



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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NASARIN RIYAH

September 2015

Chairman : Eusni Rahayu Mohd.Tohit, MPath
Faculty : Medicine and Health Science

Obesity is one of the main worldwide epidemics that leads to increase in serious health problems and reducing life expectancy. In solving this problem on obesity various missions have been executed on obesity by international health services recently. According to the latest reports, the prevalence of obese and overweight individuals have increased in most East Asian countries including Malaysia. Obesity increases the probability of various chronic diseases; exclusively type 2 diabetes mellitus, certain kinds of cancers, hypertension, dyslipidaemia and cardiovascular disease (CVD). Obesity also plays a pivotal role in the development of low-grade inflammation. In this way, some cytokines, hormones, transcription factors, bioactive lipids and signaling proteins have both immune and metabolic roles. Thus, in this study, we measured the levels of two cytokines, sCD40L and sP-selectin that can alter platelet function and play a major role in the pathogenesis of obesity-induced inflammation. Leptin another factor of interest that contributes to the pro-thrombotic state in obesity is also examined in this study. To evaluate the effects of platelet related cytokines and platelet parameters in obese respondents and its association with leptin in comparison with normal body mass index respondents, a cross-sectional study was conducted in 112 healthy normal, overweight and obese respondents of both genders in three different races groups (Malay, Chinese and Indian), aged 18 to 60 years old from August 2014 to November 2014. Respondents in this study were given a verbal explanation of the study and a respondent information sheet before signing a standardised consent form as evidence of written approval. Anthropometric variables, BMI and waist circumference (WC) were measured. The respondents were further divided into specified groups based on WHO criteria for BMI in Asian population. The control group comprised of respondents with normal BMI ($18.5\text{kg}/\text{m}^2$ - $22.9\text{ kg}/\text{m}^2$) whereas the case group included respondents with BMI between $23\text{ kg}/\text{m}^2$ to $35\text{ kg}/\text{m}^2$ (overweight and obese). A patient's pro-forma form was used to encompass information of the respondents. such as sociodemographic characteristics, family history, medical history, current medications, and some risk factors known to play a role in inflammation such as smoking, allergy history and alcohol consumption. Ten (10) milliliter of blood was drawn from the antecubital fossa by an expert phlebotomist and entered into

appropriately labeled tubes whereby three (3) ml were in the EDTA tube for full blood count (FBC) measuring MPV (Mean Platelets Volume) and platelets count, whilst the remainder 7 ml was placed in plain tubes for evaluating sCD40L, leptin and sP-selectin by ELISA analysis. A total number of 56 cases and 56 controls were compared based on their BMI levels in the final analysis. There was a significant difference in the means of weight, height, BMI and WC between case and control groups ($P<0.05$). Most of the respondents who participated in our study were Malays (54.5%) followed by Chinese (26.8%) and Indians (18.7%). Sixty-one (54.5 %) respondents were female and 45.5% were male. The analysis of MPV, sCD40L, leptin and sP-selectin showed a statistically significant difference between obese, overweight and normal weight respondents ($p<0.05$). Based on our data, there was a significant difference in the mean of PLT between overweight females and males ($p=0.005$) also a significant difference in the mean of sCD40L between these two groups ($p=0.02$). Women had higher means of sCD40L, leptin, sP-sel and platelets count than men. In contrast, males had higher amount of MPV than females. In addition, a significant correlation was reported between the levels of sP-selectin with BMI ($r=0.36$, $p=0.001$) and WC ($r=0.25$, $p=0.007$). Also there was a statistically significant correlation between MPV with BMI ($r=0.2$, $p=0.001$) and WC ($r=0.2$, $p=0.003$). Our data showed that healthy fasting obese and overweight respondents have significantly higher levels of MPV than non-obese respondents. Increase MPV indicates that, platelets are more reactive in respondent with obesity. In addition, we found that obese respondents have higher level of sCD40L compared to overweight and normal groups, suggesting a pro-inflammatory state in obese respondents. A higher MPV and sP-sel level in obese respondents than overweight and normal weight indicates a higher aggregating activity of platelets in obesity. Level of leptin concentrations found to be correlating with BMI in healthy obese and non-obese respondents. Since leptin is a factor known to induce platelet activation and aggregation, thus it can increase the cardiovascular risks as well. In addition, an association of leptin with thrombosis and haemostatic disorders in obesity has been suggested. At the end of the study, we found no significant correlations between PLT, MPV and leptin with sP-sel and sCD40L. Therefore, it has not yet been established whether elevated platelet counts in obese respondents are associated with platelet activation. But we can suggest that obesity is accompanied by platelet activation and inflammation. Present study suggests determining the association between current markers with genetic and lipid profiling by future studies to disclose the risk of CVD by these markers in obese respondents.

Abstrak tesis yang telah dikemukakan kepada Senat Universiti Putra Malaysia bagi memenuhi syarat Ijazah Master Sains

BIOOPENANDA PLATELET DAN LEPTIN DIKALANGAN WARGA MALAYSIA DENGAN BERAT BADAN BERLEBIHAN DAN OBES DI SEBUAH UNIVERSITI AWAM

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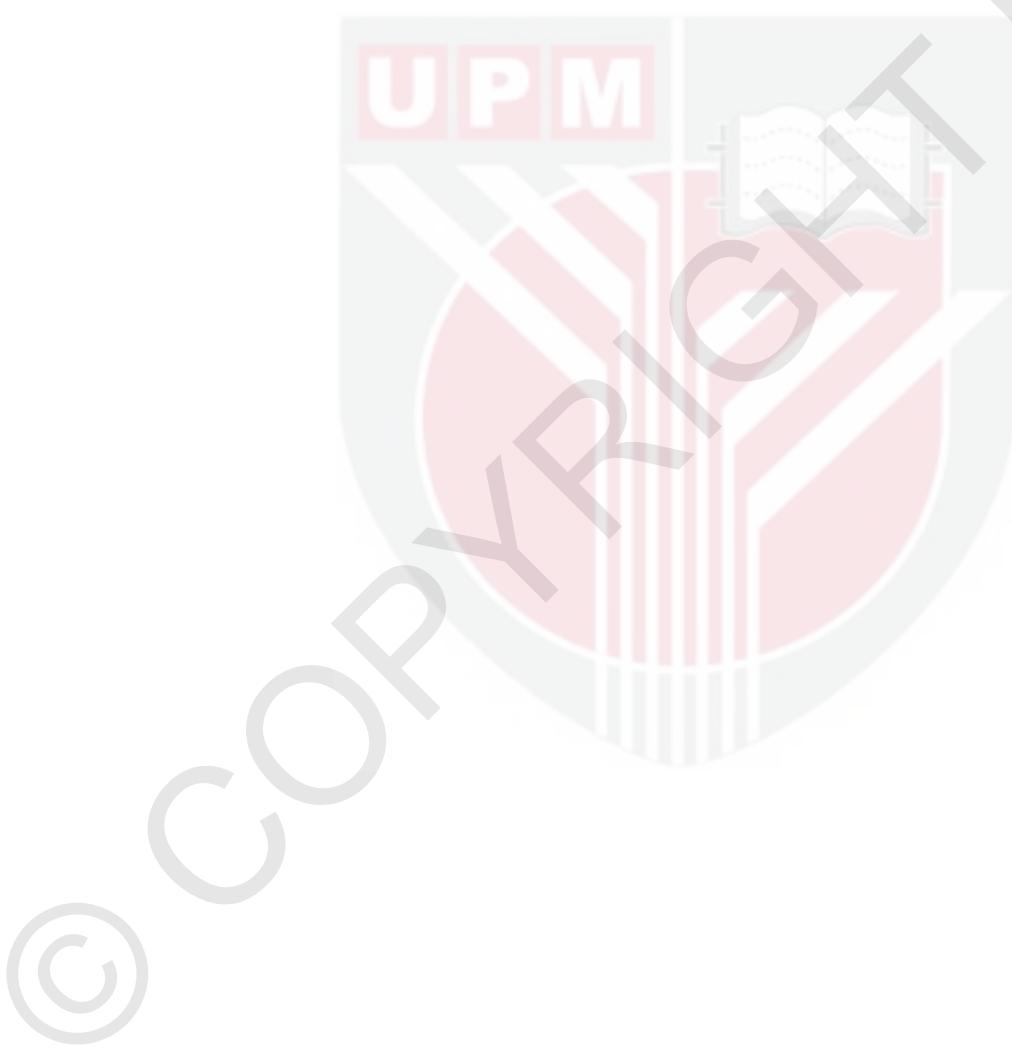
Obesiti merupakan salah satu daripada wabak utama di seluruh dunia yang membawa kepada peningkatan masalah kesihatan yang serius dan pengurangan jangka hayat. Sehingga kini, bagi menyelesaikan masalah obesiti pelbagai misi berkaitan obesiti sedang dilaksanakan melalui perkhidmatan kesihatan antarabangsa. Berdasarkan laporan terkini, kelaziman bagi subjek yang obes dan mempunyai berat badan berlebihan telah meningkat di kebanyakan negara-negara Asia Timur di mana Malaysia telah menjadi lebih terkehadapan di dalam obesiti. Obesiti didapati meningkatkan kebarangkalian menghidapi pelbagai penyakit kronik; diabetis melitus jenis 2, beberapa jenis kanser, hipertensi, dislipidemia dan penyakit kardiovaskular (CVD). Obesiti juga memainkan peranan penting bagi menyebabkan tahap inflamasi yang rendah. Bagi tindakan ini, sebahagian sitokin, hormon, faktor transkripsi, bioaktif lipid dan isyarat protein mempunyai peranan sebagai imun dan metabolismik. Faktor lain yang juga menyumbang kepada peningkatan risiko CVD adalah fungsi platelet. Oleh itu, di dalam kajian ini, kami telah menyukat tahap bagi dua sitokin sCD40L dan sP-selektin yang boleh merubah fungsi platelet dan memainkan peranan penting di dalam patogenesis bagi obesiti-mencetus inflamasi. Faktor lain yang turut dilakukan kajian adalah leptin yang didapati menyumbang kepada keadaan pro-trombotik di dalam obesiti. Untuk menilai kesan sitokin berkaitan platelet dan parameter platelet di dalam responden obes serta perkaitannya dengan leptin di dalam perbandingan di antara Indeks Jisim Badan normal bagi responden. Kajian persilangan telah dilakukan terhadap 112 responden yang normal sihat, berlebihan berat badan dan obes, kedua-dua jantina bagi tiga kumpulan kaum yang berbeza (Melayu, Cina dan India), umur di antara lingkungan 18 hingga 60 tahun daripada Ogos 2014 sehingga November 2014. Peserta yang terlibat di dalam kajian ini telah diberikan borang maklumat serta penerangan secara lisan sebelum menandatangani borang persetujuan sebagai bukti bertulis. Ukuran telah dilakukan bagi pembolehubah antropometrik, BMI dan ukur lilit pinggang. Responden seterusnya dibahagikan kepada dua kumpulan khusus bagi BMI dalam populasi Asia berdasarkan kriteria WHO. Kumpulan kawalan mengandungi individu dengan BMI normal ($18.5\text{kg}/\text{m}^2$ - $22.9\text{ kg}/\text{m}^2$) manakala kumpulan kajian terdiri daripada responden dengan BMI di antara $23\text{ kg}/\text{m}^2$ to $35\text{ kg}/\text{m}^2$ (berat

berlebihan dan obes). Borang pro-forma pesakit telah digunakan bagi mengumpul maklumat subjek seperti ciri sosiodemografik, sejarah keluarga, sejarah perubatan, rawatan perubatan terkini, dan beberapa faktor risiko yang dikenalpasti memainkan peranan di dalam inflamasi seperti merokok, sejarah alergi serta pengambilan alkohol. Sebanyak 10 milliliter darah telah dikeluarkan daripada fosa antekubital oleh plebotomis terlatih dan dimasukkan ke dalam tiub berlabel dimana 3 ml di dalam tiub EDTA untuk pengukuran darah penuh (FBC) bagi mengukur purata isispadu platelet (MPV) dan pengiraan platelet manakala lebihan darah sebanyak 7ml akan dimasukkan ke dalam tiub kosong bagi menilai sCD40L, leptin dan sP-selectin dengan menggunakan analisis ELISA. Di dalam analisis akhir, sebanyak 56 kes dan 56 kawalan telah dilakukan perbandingan berdasarkan paras BMI masing-masing. Didapati terdapat perbezaan yang signifikan di dalam purata bagi berat, tinggi, BMI dan WC di antara kumpulan kes dan kawalan ($P<0.05$). Kebanyakan responden yang terlibat di dalam kajian ini terdiri daripada Melayu (54.5%), diikuti oleh Cina (26.8%) dan India (18.7%). Enam puluh satu (54.5%) peserta adalah terdiri daripada perempuan dan 45.5% adalah terdiri daripada lelaki. Analisis bagi MPV, sCD40L, leptin and sP-selectin menunjukkan perbezaan statistik yang signifikan di antara responden yang obes, berlebihan berat badan dan berat badan normal ($p<0.05$). Berdasarkan daripada data yang diperolehi, terdapat perbezaan purata PLT yang signifikan di antara perempuan dan lelaki yang mempunyai berat badan berlebihan ($p=0.005$) juga bagi perbezaan purata sCD40L di antara kedua-dua kumpulan ini ($p=0.02$). Perempuan didapati mempunyai purata CD40L, leptin, sP-sel dan bilangan platelet yang lebih tinggi berbanding lelaki Secara berbeza, lelaki mempunyai nilai MPV yang lebih tinggi berbanding perempuan. Sebagai tambahan, korelasi signifikan telah dilaporkan di antara paras sP-selectin dengan BMI ($r=0.36$, $p=0.001$) dan WC ($r=0.25$, $p=0.007$). Juga turut terdapat korelasi signifikan secara statistik di antara MPV dengan BMI ($r=0.2$, $p=0.001$) and WC ($r=0.2$, $p=0.003$). Data menunjukkan bahawa responden obes sihat dan berpuasa serta berlebihan berat badan mempunyai paras MPV yang tinggi berbanding responden yang tidak obes. Peningkatan MPV menunjukkan bahawa platelet lebih reaktif di dalam responden yang obes. Sebagai tambahan, didapati responden yang obes mempunyai paras sCD40L lebih tinggi berbanding kumpulan responden yang mempunyai berat badan normal dan berat badan berlebihan, ini mencadangkan responden obes berada di dalam keadaan pro-inflamatori. Paras MPV dan sP-sel yang lebih tinggi bagi responden obes berbanding responden yang berlebihan berat badan serta berat badan normal menunjukkan bahawa aktiviti agregasi platelet adalah lebih tinggi di dalam individu obes. Paras kepekatan leptin didapati mempunyai hubungan dengan BMI bagi responden obes sihat dan tidak obes. Memandangkan leptin telah dikenalpasti sebagai satu faktor yang mengaruh kepada pengaktifan dan agregasi platelet, maka ia juga boleh meningkatkan risiko menghadapi kardiovaskular. Sebagai tambahan, perkaitan di antara leptin dengan kegagalan hemostatik dan thrombosis di dalam obesiti telah dicadangkan. Di akhir kajian, didapati tiada korelasi yang signifikan di antara PLT, MPV dan leptin bersama sP-sel and sCD40L. Oleh itu, masih tiada kajian yang dapat menunjukkan bahawa bilangan platelet bagi responden obes mempunyai kaitan di dalam pengaktifan platelet. Tetapi kami telah mencadangkan bahawa obesiti turut berkaitan dengan pengaktifan platelet dan inflamasi. Hasil kajian ini mencadangkan bahawa kajian susulan perlu dilakukan bagi mengenalpasti perkaitan di antara penanda genetik dan profil lipid dengan penanda kajian bagi menentukan risiko CVD oleh penanda ini di dalam responden obes.

ACKNOWLEDGEMENT

I would like to express my sincere appreciation to my supervisor: Dr Eusni Rahayu Mohd.Tohit and my co supervisors: Dr. Subashini C. Thambiah and Dr. Zuriati Ibrahim. I am really grateful for providing me such a precious opportunity to be part of this research. Especially, I am deeply honored to collaborate with Dr.Eusni Rahayu Mohd.Tohit who devoted her time, patience, and understanding during my program.

My gratitude also goes to the Haematology and pathology Lab staff. There are not enough words to describe your excellent help.



I certify that a Thesis Examination Committee has met on 14 September 2015 to conduct the final examination of Nasrin Riyahi on her thesis entitled "Platelet-Related Biomarkers and Leptin Levels in Overweight and Obese Malaysians in a Public University" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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TABLE OF CONTENTS

	Page
ABSTRACT	i
ABSTRAK	iii
ACKNOWLEDGEMENTS	v
APPROVAL	vi
DECLARATION	viii
LIST OF TABLES	xii
LIST OF FIGURES	xiii
LIST OF ABBREVIATIONS	xiv
 CHAPTER	
1 INTRODUCTION	1
1.1 Background	3
1.2 Problem statement	4
1.3 Significance of Study	4
1.4 Objectives	4
1.4.1 Main Objectives	4
1.4.2 Specific Objectives	4
1.5 Study Hypothesis	5
2 LITERATURE REVIEW	6
2.1 Obesity	6
2.1.1 Definition	6
2.1.2 Prevalence	8
2.2 Obesity, Inflammation, and Cardiovascular Risk	9
2.3 Factors associated with Obesity	10
2.3.1 Ethnicity	10
2.3.2 Gender	10
2.3.3 Platelet	11
2.4 Alterations of platelet function in obesity	14
2.5 Specific platelet-related biomarkers and parameters involved in obesity	15
2.5.1 sCD40L	15
2.5.2 sP-selectin	16
2.5.3 Mean platelet volume and obesity	18
2.6 Leptin	20
3 METHODOLOGY	22
3.1 Ethic approval	22
3.2 Type of study	22
3.3 Study duration	22
3.4 Location	22
3.5 Sampling	22
3.5.1 Respondents recruitment	22
3.5.2 Sampling size and population	23

3.5.3	Criteria	24
3.6	Data Collection Procedure	24
3.7	Clinical Assessment	25
3.8	Blood Sampling	25
3.9	Laboratory Investigations	25
3.9.1	Full Blood Count (FBC)	25
3.9.2	ELISA Principle Basis and Extension	26
3.10	Statistical analysis	27
4	RESULTS	28
4.1	Baseline Characteristics among Participants	28
4.2	Sociodemographic characteristics of study population	28
4.3	Laboratory parameters (platelet count, MPV, platelets related cytokines and serum leptin) between normal BMI, overweight and obese respondents	30
4.4	Laboratory parameters (platelet count, MPV, platelets related cytokines and serum leptin) between normal BMI, overweight and obese respondents by gender	32
4.5	Correlation between Laboratory Parameters with WC and BMI	33
4.6	Association between platelet related cytokines with MPV, PLT and leptin	34
5	DISCUSSION	35
5.1	General Characteristics	35
5.2	Levels of platelet count, MPV, platelets related cytokines (sCD40L and sP-selectin) and serum leptin between obese, overweight and normal BMI individuals	35
5.2.1	Changes in level of MPV and platelets in obese and non-obese group	35
5.2.2	Changes in the level of sCD40L	36
5.2.3	Changes in the level of sP-selectin	37
5.2.4	Changes in level of leptin in obese and non-obese group	38
6	CONCLUSION	40
6.1	Limitation of study	41
6.2	Future studies	41
REFERENCES		42
APPENDICES		59
BIODATA OF STUDENT		99

LIST OF TABLES

Table		Page
4.1	Sociodemographic characteristics of study population	29
4.2	Sample distribution based on Categorised BMI (CBMI)	29
4.3	Age and anthropometric characteristics between normal BMI, overweight and obese respondents	30
4.4	Laboratory parameters of study population	30
4.5	Correlation test between age and markers	31
4.6	Laboratory parameters (platelet count, MPV, platelets related cytokines and serum leptin) between normal BMI, overweight and obese respondents	31
4.7	The effect of gender and BMI groups on laboratory parameters (platelet count, MPV, platelets related cytokines and serum leptin)	32
4.8	Laboratory parameters (platelet count, MPV, platelets related cytokines and serum leptin) between genders in normal BMI, overweight and obese respondents	33
4.9	Pearson correlation test between laboratory parameters with WC and BMI	34
4.10	Pearson correlation test between cytokines and MPV, PLT Leptin	34

LIST OF FIGURES

Figure		Page
2-1	WHO (2004) BMI Classification among Asian population	8
2-2	Secreted products intervene in inflammation and its role in obesity	13
2-3	Interactions between P-selectin, platelets, leucocytes and atherogenesis	17



LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
ADP	Adenine di-Phosphate
APCs	Antigen presenting cells
BMI	Body mass index
CV	Cardiovascular
CVD	Cardiovascular disease
CRP	C-reactive protein
Ca ⁺²	Calcium
CBMI	Categorised body mass index
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked Immunosorbent Assay
FVa	Activated factor V
FXa	Activated factor X
FBC	Full blood count
fL	Femtolitre
GPIb	Glycoprotein Ib
GPIIb	Glycoprotein IIb
GPIV	Glycoprotein IV
IL-6	Interleukin 6
ICAM-1	Intercellular Adhesion Molecule 1
kg/m ²	Kilogram/ square meter
MPV	Mean platelet volume
mRNA	Messenger ribonucleic acid
NHANES	National Health and Nutrition Examination Survey
NHMS	National Health and Morbidity Survey
NO	Nitric oxide
PLT	Platelet
PADGEM	Dependent granule external membrane protein
PAI-1	Plasminogen activator inhibitor-1
PECAM-1	Platelets endothelial cell adhesion molecule
PGI ₂	Prostaglandin I2
Psgl-1	P-selectin glycoprotein ligand-1
RBC	Red blood count
ROS	Reactive oxygen species
STEMI	ST-elevation myocardial infarction
SLE	Systemic lupus erythematosus
SD	Standard deviation
sCD40L	Soluble CD40 ligand
sP-selectin	Soluble p-selectin

TNF α	Tumor necrosis factors α
TXA2	Thromboxane A2
Th1	T helper cell
vWF	Von Willebrand factor
WBC	White blood count
WHO	World Health Organization
WC	Waist circumference



CHAPTER 1

INTRODUCTION

1.1 Background

Undoubtedly, one of the main worldwide epidemics that leads to various considerable health problems is obesity, which has recently attracted the international community's attention (Hall et al., 2002). In 2005, World Health Organization (WHO) stated that there were almost 1.6 billion obese and overweight people aged 15 years and above. In a subsequent project by WHO in 2015, it is estimated that, there are close to 2-3 billion overweight adults and approximately 700 million obese people (WHO 2006). Over the past year, the number of obese and overweight people increased in the most countries in Asia whereas this value is deferent between these countries. Malaysia is considered as a multiple ethnic country which has been recognized as the highest for obesity among Asian countries (Yoon et al., 2006). Approximately, half of the Malaysian women and almost 45% of men are overweight or obese (Wan Mohamud et al., 2011). Thus, the obesity prevalence, the obesity significance and the economic costs of the disease create an urgent need for better therapeutics and understanding of the physiological processes that balance energy intake and energy expenditure. Moreover, comprehensive studies uphold the fact that obesity and being overweight has been nominated as the fifth leading risk of global mortality and one of the main important criteria in various chronic diseases, including psychological deficits (Milaneschi et al., 2012), type 2 diabetes mellitus (Vogt & Brüning, 2013) and some malignancies (Speakman, 2008) such as breast cancer (Amitani, Asakawa, Amitani, & Inui, 2013) and colorectal cancer (Na & Myung, 2012).

More importantly, obesity can be considered as one of the autonomic risk factor in cardiovascular disease (CVD) (McLaughlin et al., 2007). CVD is the most intense major factor contributing to more than one-third of morbidity in developed and developing countries such as Malaysia (WHO 2000).

Body Mass Index (BMI) is a simple and well known method for assorting people as normal, overweight or obese based on two characteristics; height in meters squared (m^2) and body weight in kilograms (kg). However, BMI is not suitable for certain individuals like athletes with increased muscle mass and the elderly. For this reason waist circumference (WC) is a more appropriate index of numerical measurement rather than BMI only, especially when we used WC in conjunction with BMI. There is some evidence showing that WC and BMI in combination can predict related health risks in obesity better than BMI alone (Zhu et al., 2002).

Obesity is considered a multifactorial and complex disease. In addition to the energy accumulation and environmental factors, genetics are also involved in obesity (Piché et al., 2005). Since the metabolic and immune systems are closely linked and relevant, any storage and excessive consumption of nutrient has the potential to overload signaling networks, and this overload can affect these systems (Plutzky, 2009). In this way, a lot of cytokines, hormones, transcription factors, bioactive lipids and signaling proteins have both immune and metabolic roles (Wellen & Hotamisligil, 2005). Thus, these immune systems and regulatory mechanisms interact with human disease. There are some evidence from clinical observations in *in vitro* studies demonstrating that metabolic dysfunction and obesity are correlated with a low grade chronic inflammatory state (Heilbronn & Campbell, 2008).

The presence of a prothrombotic state accounts in part for the high prevalence of cardiovascular (CV) events in patients with obesity, despite the control of traditional risk factors (Santilli et al., 2012). Recent studies focused the attention on the pathogenic role of platelet hyperactivation (Davì & Patrono, 2007). Platelets play some crucial role in elevating CV risk in obesity which shows increased activity and decreased sensitivity to the some pharmacological and physiological anti-aggregating factors (Stein, Beemath, & Olson, 2005). Furthermore, platelets contribute to inflammation, atherogenesis and atherothrombosis. Platelets are also attached to the damaged vessels by accumulating at sites of vascular injury and releasing bioactive moderators (Michelson, 2004).

Recently, sCD40L a new inflammatory marker has been found in platelets. sCD40L is a part of the tumor necrosis family and a trans-membrane protein which is also found on T helper cells and vascular smooth muscle cells (Uwe Schönbeck et al., 2001). With respect to obesity as a proinflammatory state, this connectivity between sCD40L and obesity is a young and probable region of research.

Another marker of interest is soluble P-selectin (sP-sel) because of its role in modulating interactions between blood cells and the endothelium, and also because of the possible use of the soluble form as a plasma predictor of adverse CV events (Blann, Nadar, & Lip, 2003). Soluble P-selectin is a transmembrane protein synthesised by platelets and endothelial cells and stored in intracellular granules to be expressed on the plasma membrane only upon cell activation (Lim, Blann, & Lip, 2004).

One of the specific changes in obesity is the amount of leptin hormone which is produced by white adipose tissue. Leptin is one of the most numerous adipocyte products and has a substantial effect on platelet activation and the immune system (Kazmi et al., 2013). It has been shown that the receptor of leptin is expressed in platelets (Nakata, Yada, Soejima, & Maruyama, 1999). A number of studies on promoting platelet aggregation by leptin have been conducted, (Konstantinides, Schäfer, Koschnick, & Loskutoff, 2001) that specify a conceivable direct connection between leptin, thrombotic complication and obesity.

Based on previous research, mean platelet volume (MPV) is a novel parameter that has been demonstrated to be consistently linked to CV events (Park, Schoene, & Harris, 2002) and is also a determinant of platelet activation (Hekimsoy, Payzin, Örnek, & Kandoğan, 2004). However, the increment in MPV as a determinant of platelet activation and how this can affect the CV events have not been clarified. There are three possible hypotheses regarding the increased platelet activation; (i) arterial wall injury; (ii) circulating inducers of platelet activation; and (iii) genetic predisposition (van der Loo & Martin, 1999). However, only few studies have been conducted on MPV and its relation to obesity. Therefore, the present study proposes to compare MPV levels in healthy obese and non-obese respondents.

The interpretation of the relationship between platelet activation and higher platelet units is still undefined. An adverse clinical result has been seen in patients with ST-elevation myocardial infarction (STEMI) with respect to higher platelet units (Ly et al., 2006). Another study has indicated that there is a correlation between the risk of stroke and platelet activation or specifically leukocyte-platelet complex formation and higher platelet units in carotid-stenosis patients (McCabe et al., 2005). It has been demonstrated that platelet count and platelet activation are connected to patients with chronic inflammation including patients with essential thrombocytosis (Jan Jacques Michiels, Ten Kate, Koudstaal, & Van Genderen, 2013), and patients with inflammatory bowel disease (Collins & Rampton, 1997). While obesity is known as a state of chronic inflammation (Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000), there are still several ongoing arguments about the correlation between platelet activation and body fat.

1.2 Problem statement

Obesity and overweight are escalating and raising considerable public concern because they increase the prevalence of severe cardiovascular events and other systemic diseases, causing great costs and burden to both society and families (Zhou et al., 2012). Based on the last National Health and Morbidity Survey 2011, obesity prevalence in individuals ≥ 18 years of age has significantly increased since 1996 by 280% (Azmi Jr et al., 2009). In Malaysia, at the population level, a high prevalence of obesity results from a complex interaction between changes in the population's lifestyle, involving a higher energy and fat consumption and an increasingly sedentary lifestyle (WHO, 2000). Recent studies have shown that obesity is closely related to a low-grade inflammatory state and a prothrombotic condition as well (Guldiken et al., 2007). Furthermore, there is an ongoing debate on whether obesity increases this propensity to thrombosis. To address these issues, we measured the level of some cytokines related to platelet activation and inflammation in respondents with different degrees of body mass index (BMI).

1.3 Significance of Study

This notion that chronic inflammation can be linked with metabolic dysfunction and obesity has become more acceptable in recent years. Metabolic dysfunction is suggested as an immune inflammatory disturbance, induced either by excess feeding or obesity, malnutrition, and starvation. This study also provides outcomes that can be useful in further research on biomarkers involvement of pathogenesis in obesity and the risk of cardiovascular. To the best of our knowledge, there is no exact data regarding the association between genders with obesity biomarkers, therefore results of the current study might provide beneficial information on future studies related to gender as part of contributing factor in obesity. This study will be the first in the Malaysian population in determining the relevance between platelet parameters and levels of leptin hormone and inflammatory markers such as sCD40L and sP-selectin in obesity. This study will provide a database for future research in relation to obesity, particularly in our multiethnic Malaysian population.

1.4 Objectives

1.4.1 Main Objectives

To determine the relationship between platelet related cytokines (sCD40L, sP-selectin), platelet parameters (platelet count, MPV) and leptin with obesity in University Putra Malaysia

1.4.2 Specific Objectives

1. To compare the levels of platelet count, MPV, platelets related cytokines and serum leptin between obese, overweight and normal BMI individuals
2. To determine the relationship between MPV and platelet count with platelet related cytokines in obese, overweight and normal BMI individuals
3. To analyze association between BMI and waist circumference with platelet related cytokines, platelet parameters and leptin amongst the normal, overweight and obese population as well as the association between platelet related cytokines with serum leptin and platelet parameters.
4. To compare the levels of platelet count, MPV, sCD40L, sP-selectin and serum leptin between different genders by categorized BMI

1.5 Study Hypothesis

- x Higher means of sCD40L and sP-selectin, platelet count, MPV and leptin seen in the obese group than in the non-obese group
- x There is an association between platelets activation and platelets count in obese and normal BMI respondents
- x Women have higher amount of sCD40L and sP-selectin, platelet count, MPV and leptin than men

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