HIGH SENSITIVITY C-REACTIVE PROTEIN LEVELS AND BLOOD PRESSURE STATUS IN YOUNG ADULTS

BY

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ABSTRACT

C-Reactive Protein (CRP) levels had been recommended in the global risk prediction for cardiovascular diseases (CVD) of asymptomatic individuals. CRP levels vary substantially across diverse population worldwide. Thus, identifying its normal values in our population is necessary for its accurate use as a better predictor of future cardiovascular events and allowing an earlier initiation of preventive measures. This comparative cross sectional study was conducted to compare the hs-CRP concentrations in different categories of blood pressure among young adults (18 and 45 years old) in Kuantan, Pahang, Malaysia. A total of 272 subjects were recruited and categorised into three groups namely normotensive (NT), prehypertensive (PHT) and hypertensive (HPT) according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Samples were assayed for hs-CRP profile using Siemens Advia 2400 Chemistry System Analyser based on polyethylene glycol (PEG)-enhanced immunoturbidimetric method. The hs-CRP levels of subjects differ between populations in some countries. There was a significant difference between the three groups. The mean (SD) of hs-CRP for NT was 0.77 (1.39) mg/L, PHT and HPT were 1.54 (1.28) mg/L and 2.15 (1.30) mg/L respectively. Hs-CRP was not significantly associated with blood pressure status after adjustment for covariates in this study, however the relationship was confounded by other factors that were age, gender, parent's history of hypertension and BMI status. The risk of developing cardiovascular diseases in 10 years' time was highest in the hypertensive young adults. The predictive value of CRP Risk alone is just as accurate as newly adapted Reynolds Risk Score, in the hypertensive young adults, but not in the prehypertensive young adults. The findings of the study suggest the importance of developing our own rubric on cardiovascular risk assessment based on blood pressure and hs-CRP particularly in young adults.

ملخص البحث

يُنصح بمستويات البروتين المتفاعل-C في التنبؤ بمخاطر أمراض القلب والأوعية الدموية عالميا للأفراد عديمي الأعراض. مستويات البروتين المتفاعل -C تتباين بشكل كبير بين مختلف السكان في جميع أنحاء العالم. وبالتالي، فإن تحديد قيمه الطبيعية في مجتمعنا ضروري من أجل الإستخدام الصحيح له كمؤشر تنبوئي أفضل لأمراض القلب والأوعية الدموية في المستقبل والذي يسمح ببدء مبكر للتدابير الوقائية. وقد أُجريت هذه الدراسة المقطعية المقارنة لمقارنة تركيزات البروتين المتفاعل-C العالي الحساسية بين الشباب (18-45 سنة) ذوي المستويات المختلفة لضغط الدم في كوانتان، باهانغ، ماليزيا. عدد الأشخاص الذي وظفوا فى هذه الدراسة هو 272 وتم تصنيفهم إلى ثلاث مجموعات هي ضغط الدم الطبيعي، ما قبل فرط ضغط الدم وفرط ضغط الدم وفقا للتقرير السابع للجنة الوطنية المشتركة للوقاية والكشف والتقييم، وعلاج ارتفاع ضغط الدم (JNC 7). تم فحص عينات البروتين المتفاعل-Cالعالي الحساسية باستخدام جهاز التحليل الكيميائي سيمنز أدفيا 2400 والذي يعتمد على طريقة العكر المناعي المحسن بالبولي ايثيلين جلايكول. مستويات البروتين المتفاعل-C عالي الحساسية تختلف بين السكان في بعض البلدان.كان هناك فرق إحصائي ذو اعتبار بين المجموعات الثلاث. متوسط البروتين المتفاعل-C عالي الحساسية لمجموعة ضغط الدم الطبيعي كان 0.77 (1.39) ملجم/لتر، و لمجموعتي ما قبل فرط ضغط الدم وفرط ضغط الدم كان 1.54 (1.28) ملجم/لتر و 2.15 (1.30) ملجم/لتر على التوالي. لم يظهر أي ارتباط ذو أهمية إحصائية بين البروتين المتفاعل-C عالي الحساسية وحالة ضغط الدم بعد تعديل المتغيرات في هذه الدراسة، وبالرغم من ذلك فإن العلاقة تأثرت بعوامل أخرى متمثلة فى العمر والجنس وما إذا كان الوالدان مصابين بارتفاع ضغط الدم وحالة مؤشر كتلة الجسم. خطر الإصابة بأمراض القلب والأوعية الدموية خلال العشر سنوات الماضية كان الأعلى بين الشباب المصابين بارتفاع ضغط الدم. القيمة التنبؤية للمخاطر باستخدام البروتين المتفاعل -C دقيقة بحد ذاتها تماما مثل مسجل رينولدز للمخاطر المتبنى حديثا، وذلك في الشباب الذين يعانون من فرط ضغط الدم، ولكن ليس في الشباب في مرحلة ما قبل فرط ضغط الدم. وتشير نتائج الدراسة إلى أهمية تطوير المعايير الخاصة بنا لتقييم مخاطر أمراض القلب والأوعية الدموية اعتمادا على ضغط الدم و البروتين المتفاعل-C العالي الحساسية خاصة في الشباب.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Medical Sciences

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DECLARATION

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DEDICATION

This dissertation is dedicated to my late parents for laying the foundation of what I turned out to be in life. Their loves and memories will remain in my heart forever and ever.

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LIST OF ABBREVIATIONS

Ang II	Angiotensin II
ANOVA	Analysis of Variance
BMI	Body Mass Index
CDC-AHA	Centers for Disease Control and Prevention and the American Heart Association
CI	Confidence Interval
CIOMS	Council for International Organization of Medical Sciences
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trial Unit
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
df	degree of freedom
ELISA	enzyme-linked immunosorbent assay
FBS	Fasting blood sugar
FEME	Full Examination, Microscopic Examination
FRGS	Fundamental Research Grant Scheme
HbA1c	Hamoglobin A1c
HDL	High density lipoprotein cholesterol
HPT	hypertensive
Hs-CRP	high sensitivity C-Reactive Protein
ICH-GCP	International Conference of Harmonisation, Good Clinical Practice
IHD	Ischaemic heart disease
JNC	The Seventh Report of the Joint National Committee
LDL	Low density lipoprotein cholesterol
mCRP	monomeric C-Reactive Protein
MMP	metalloproteinases
MREC	Malaysia Research Ethics Committee
NHANES	National Health and Nutrition Examination Survey
NHMS	National Health Morbidity Survey
NO	Nitric oxide
NT	normotensive
OR	odds ratio
PAI-1	Plasminogen Activator-Inhibitor 1
PASS	Power Analysis and Sample Size
pCRP	pentameric C-Reactive Protein
PHT	prehypertensive
RAAS	Renin-Angiotensin-Aldosterone System
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SD	standard deviation
SE	standard error
TG	triglyceride
tPA	tissue plasminogen activator
WHO	World Health Organisation

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Cardiovascular diseases (CVD) remain the leading cause of mortality around the world. Out of 54 million deaths, CVD alone accounts for about 30 per cent or approximately 17 million deaths (Feigin et al., 2016; World Health Organization, 2015). The majority of these cardiovascular deaths were attributed to either ischaemic heart disease (IHD) or cerebrovascular disease. Report from the Global Burden of Cardiovascular Disease (Feigin et al., 2016) indicates that cardiovascular mortality rates have declined dramatically over the past two decades, however the number of life years lost to premature cardiovascular deaths is increasing in low- and middle-income regions of the world.

Multiple factors are associated with the development of CVD. The well-known Framingham Heart Study began in 1948 and followed through for almost half of a century was essential in identifying risk factors of CVD. These include both non-modifiable and modifiable risk factors such as genetic and age factors as well as elevated blood pressure, smoking, obesity, increased blood sugar and hyperlipidaemia. Significant insight from this epidemiological study also brought about an association between hypertension and CVD (Franklin & Wong, 2013).

Apart from the well-known conventional risk factors, subclinical biomarker such as C-Reactive Protein (CRP) has gained much attention and being widely studied across the world on its role in the development of atherosclerosis. Previously, the link between CRP and CVD is thought to be indirect, where the circulating CRP only

reflects the extent of the acute phase reaction in response to non-specific stimuli of an inflammatory process (Lagrand et al, 1999). However, growing evidences indicate that CRP has a greater role than just as an indicator of an acute phase reaction. Low grade chronic inflammation, characterized by elevated plasma concentration of CRP is associated with an increased risk of atherosclerotic cardiovascular disease (Cleland, Sattar, Petrie, Forouhi et al, 2000). Atherosclerosis is considered as a complex inflammatory process. The inflammatory cells are thought to initiate the local weakening of the atherosclerotic plaque which results in its rupture, with the consequential formation of a thrombus and occlusion of the artery (Alexander, 1994; Munro & Cotran, 1988).

CRP exhibits multiple characteristics which suits as a CVD risk predictor. In addition, lower CRP concentration in plasma or serum can be detected using higher sensitivity methods called high-sensitivity C-Reactive Protein (hs-CRP). In 2003, The Centers for Disease Control and Prevention and the American Heart Association (CDC-AHA) recommended values of hs-CRP to be part of the global risk prediction for cardiovascular diseases in asymptomatic individuals especially in the intermediate risk group. However, it is not used as screening tool for the entire adult population.

The Reynolds Risk Score is a cardiovascular disease risk equation derived from Framingham Cardiovascular Diseases Risk Assessment which was developed and validated using data from more than 24,000 American women who were monitored over a ten-year period for the development of cardiovascular events (Ridker, Buring, Rifai, & Cook, 2007). It includes family history and hs-CRP in addition to the conventional risk factors and allows more accurate classification of patients to higher and lower risk groups (Ridker, Paynter, Rifai, Gaziano, & Cook, 2008). Hence, it improves global risk prediction of CVD events.

Hypertension is one of the major risk factors for CVD. It is responsible for at least 45 and 51 per cents of total deaths due to heart disease and stroke, respectively (World Health Organization, 2013). Across the globe, prevalence of hypertension was highest in the African Region (46%), followed by the South-East Asia Region (36%) and lowest in the Region of the America at 35% (World Health Organization, 2013). Substantial variation between ethnic groups was also reported where the non-Hispanic black adults showed the highest prevalence of hypertension, whereas non-Hispanic Asian adults displayed the lowest prevalence among all the studied groups (Yoon, Carroll, & Fryar, 2015). Furthermore, it has also been reported that CRP levels differ by ethnicity in a number of multiethnic studies conducted in a few regions of the world (Lakoski et al., 2005).

1.2 PROBLEM STATEMENT

Numerous large studies had been conducted to view the association between hypertension and CRP, as well as the development and validation of cardiovascular risk assessment tools. However, most studies were conducted among western populations in which, majority of the participants are Caucasians with age beyond 40 years old. Therefore, generalization of data might be limited to certain population only (Leonelo E Bautista, Atwood, O'Malley, & Taylor, 2004; Blake, Rifai, Buring, & Ridker, 2003). Aggregated data from Asian countries are also lacking and thus applying similar tools using CRP levels from Western countries to Asian individuals might not be justified or accurate. The study aims to assess the relationship of hs-CRP values and other cardiovascular risk factors with blood pressure status among young adults in Kuantan.

1.3 SIGNIFICANCE OF THE STUDY

Early detection of hypertension status especially in young adults provides a better prognosis and prevention of progression towards CVD events. Hs-CRP predictive values for CVD among Malaysian population may differ from other western and Asian countries. The findings of this study may suggest the need to develop our own rubric on cardiovascular risk assessment based on blood pressure and hs-CRP especially for young adults.

1.4 RESEARCH QUESTIONS

Is there any difference in CRP levels in normotensive, prehypertensive and hypertensive young adults?

1.5 RESEARCH HYPOTHESIS

There is a significant difference in hs-CRP levels in prehypertensive and hypertensive groups compared to normotensive group of young adults in Kuantan.

1.6 RESEARCH OBJECTIVES

The general objective is to assess the association between hs-CRP and different categories of blood pressure status, namely normotensives, prehypertensives and hypertensives young adults living in Kuantan.

Specific objectives are:

1. To compare the levels of hs-CRP in the normotensive, prehypertensive and hypertensive young adults groups.
2. To determine the association between hs-CRP levels and other cardiovascular risk factors and blood pressure status of the young adults.

3. To measure the risk of CVD in the young adult groups using Reynolds Risk Assessment calculator.
4. To compare the predictive values of CVD risk among the young adults using CRP only, and the Reynolds Risk Score.

CHAPTER TWO

LITERATURE REVIEW

2.1 PREVALENCE OF HYPERTENSION

Hypertension remains the leading preventable risk factor for premature mortality and morbidity worldwide (Feigin et al., 2016). It is estimated that hypertension causes 7.5 million deaths, which is about 12.8% of the total of all deaths per year (WHO, 2015). In 2015, approximately 44% of adults aged 18 and above (around 20% females and 24% males) had been diagnosed with hypertension. The number of people with the condition rose from 1 billion in 2008 to 1.13 billion in 2015 (World Health Organization, 2015).

Across the globe, the prevalence of hypertension was highest in the African Region (46%), followed by the South-East Asia Region (36%) and lowest in the Region of the America at 35% (World Health Organization, 2013). Hypertension shows a substantial variation between ethnic groups with the highest rates among African-American women (Yoon et al., 2015). Data from the National Health and Nutrition Examination Survey (NHANES) for 2011 to 2014 showed the prevalence of hypertension was highest in non-Hispanic black adults (41.2%) as compared to other ethnicities namely non-Hispanic white (28.0%), non-Hispanic Asian (24.9%), and Hispanic (25.9%) adults (Yoon et al., 2015). Comparing ten countries in South East Asia, the prevalence of high blood pressure ranged from 19% in Democratic People's Republic of Korea to 42% in Myanmar as observed in Figure 2.1 below. Data from a national health morbidity survey (NHMS) shows that in 2011, the prevalence of hypertension among Malaysians aged 18 years and above, and for aged 30 years and

above was 32.7% and 43.5% respectively (Institute for Public Health, 2011). In general, the prevalence of hypertension among adults in the United States was similar among males (30.0%) and females (29.0%), however slightly higher prevalence was found in males in almost all countries of the South-East Asia Region.

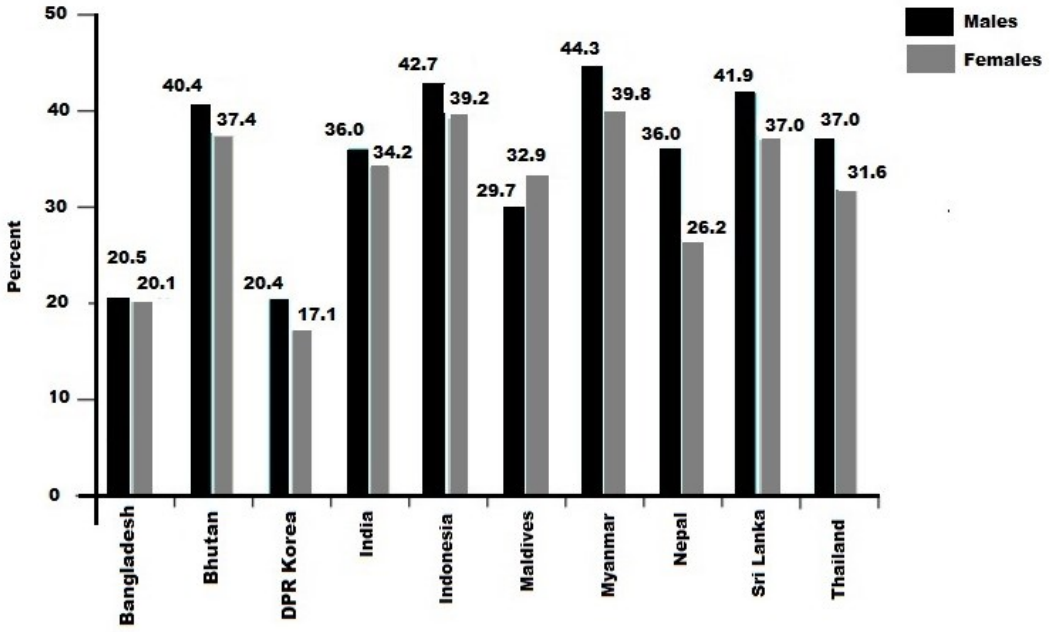

Figure 2.1 Age-standardised prevalence of hypertension in adults beyond 25 years old in South East Asia Region in 2008. Adapted from World Health Organization (2013)

Studies on hypertension have been carried out focusing not only to determine the underlying risk factors and its therapy, but further to discover preventive measures of this global burden.

2.1.1 Definition, Classification and Types of Hypertension

Blood pressure is determined by cardiac output and systemic vascular resistance. Arterial hypertension occurs either due to an increase in cardiac output, or an increase in systemic vascular resistance, or both. Systemic arterial hypertension is defined as

persistently elevated blood pressure which progresses for an interval of time, later results in impairment of the end-organs and consequentially leads to increased morbidity and mortality (Black & Elliot, 2013).

Hypertension is generally classified into two types, namely primary and secondary hypertension (Poulter, Prabhakaran, & Caulfield, 2015). Primary or 'essential' hypertension is the most common type present in the population which accounts for 90 to 95 per cent of the cases. It is defined as persistent elevation of blood pressure due to multiple non-specific lifestyle and genetic factors which exacerbate the risk of hypertension such as high intake of salt, obesity, tobacco smoking and alcohol consumption as well as genetic factors (CDC, 2016). Complex interaction between numerous pathophysiologic processes involving renal, vascular, and central mechanisms forms the basis primary hypertension.

Meanwhile, the less frequently occurring type is secondary hypertension. It generally begins at an earlier age without family history, develops through identifiable factors or as a result from other causes such as Cushing's syndrome, endocrine disorders, renovascular disease, coarctation of aorta, pheochromocytoma, or triggered by iatrogenic factors such as contraceptive pills (Beevers, 2001; Poulter et al., 2015).

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) produced in 2003 classified blood pressure into a few categories, and this was the clinical standard used in the United States and other countries for the prevention, detection, evaluation and treatment of hypertension until recently. Table 2.1 shows classification of blood pressure stages by the JNC 7 Report.

Table 2.1 Blood Pressure Staging System of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Blood pressure stage	**Blood pressure range (mm Hg)**
Normal	SBP < 120 and DBP < 80
Prehypertension	SBP 120 – 139 or DBP 80 - 89
Stage 1 Hypertension	SBP 140 – 159 or DBP 90 – 99
Stage 2 Hypertension	SBP ≥ 160 or DBP ≥ 100 mm Hg

DBP – Diastolic blood pressure, SBP – systolic blood pressure

2.1.2 Pathophysiology of Hypertension

Hypertension develops from a collection of pathophysiologic factors which include neurohormonal, vascular and cellular mechanisms (Black & Elliot, 2013). The main pathophysiologic mechanisms of hypertension are activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) and endothelial dysfunction as a result of inflammatory processes. This paper focuses on the inflammatory pathway.

2.1.2.1 Endothelial Dysfunction

Endothelium, the cellular monolayer in the inner surface of the blood vessel plays a crucial role in regulating vascular homeostasis in healthy endothelial cell condition. Regulation of vascular tone by the endothelial cells is via various release of vasoactive substances such as nitric oxide (NO), arachidonic acid metabolites, reactive oxygen species (ROS), and vasoactive polypeptides. This results in the maintenance of vascular tone and permeability, anti-inflammatory, anti-coagulation and anti-

fibrinolysis activities and cell proliferation (Vanhoutte, Shimokawa, Tang, & Feletou, 2009).

Impaired homeostasis as a result of endothelial dysfunction, produces excessive vasoconstriction which increases total peripheral resistance. The most susceptible site of increased systemic resistance due to sustained elevated pressure is the microcirculation particularly in the cerebral, ocular and renal beds (Feihl, Liaudet, Levy, & Waeber, 2008). A minute decrease in the lumen of the small arteries significantly increases resistance to blood flow. Thus, it has an essential role in the development of hypertension and complications of hypertension (Schiffrin, 1992, 1997). Additionally, low grade chronic vascular inflammation due to an impaired function of the endothelial cells causes the production of vasoconstrictor agents, adhesion molecules, and growth factors including (Ang II) and endothelin-1. Ang II is actively involved in the pathophysiology of hypertension (Durier et al., 2003; Ross, 1999). Local inflammations as well as impaired homeostasis in vascular tissues are therefore accepted as an important contributing factor to the development of hypertension, initiation and progression of atherosclerosis as well as to the development of cardiovascular diseases.

2.1.3 Complications of Hypertension

One of the most serious health problems related to untreated high blood pressure is atherosclerosis which leads to cardiovascular diseases such as ischemic heart disease, stroke, coronary artery disease, heart failure, atrial fibrillation and peripheral vascular disease. The other most common complications of hypertension is chronic renal failure (World Health Organization, 2017).

2.1.4 Hypertension as Risk Factor for CVD

The prominent Framingham Heart Study which commenced in 1948 has led to identification of multiple risk factors of CVD. Through a series of studies, the risk factors were categorised into non-modifiable and modifiable risk factors. Non-modifiable risk factors are those which are naturally occurring in an individual and cannot be reduced or controlled by intervention such as age, sex, race or ethnicity, and genetic factors. In contrast, modifiable risk factors are behavioural risk factors that can be lessened or managed by intervention, thereby decreasing the probability of disease. These include elevated blood pressure, tobacco use, raised blood glucose as in diabetes mellitus, physical inactivity, unhealthy diet, high cholesterol or lipids and overweight or obesity (O'Donnell & Elosua, 2008; Paciaroni & Bogousslavsky, 2010; WHO, 2015b). Newer risk factors such as biochemical and subclinical disease markers for instance lipoprotein (a), C-Reactive Protein, homocysteine, and markers of fibrinolytic and hemostatic function such as fibrinogen, D-dimer, tissue plasminogen activator, and plasminogen activator inhibitor-1 antigen, are also identified as risk factors for these diseases (Bassuk, Rifai, & Ridker, 2004; Wu & Tsongalis, 2001).

Table 2.2 Risk factors of cardiovascular diseases

Non-modifiable	Modifiable	Biochemical
Age	Elevated blood pressure	Lipoprotein (a)
Gender	Tobacco use	C-Reactive Protein
Race or ethnicity	Raised blood glucose	Homocysteine
Genetic factors	Physical inactivity	Fibrinolytic and haemostatic factors
	High cholesterol or lipids	
	Overweight or obesity	