HAPTOGLOBIN AND OTHER BIOMARKERS OF CORONARY ARTERY DISEASE IN YOUNG ADULTS WITH HYPERTENSION AND ACUTE MYOCARDIAL INFARCTION

BY

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ABSTRACT

Acute myocardial infraction (AMI) is the most common clinical manifestation of coronary artery disease (CAD). Young age is no longer considered a protective factor since the incidence of young adults with AMI is increasing. Hypertension is an important risk factor for CAD in young adults. Prehypertension without proper management is also associated with an increased risk of CAD. Hence, the identification of CAD biomarkers in young hypertensive and prehypertensive adults is necessary to improve risk stratification of premature AMI in these cohorts. The main objective of this study was to compare protein expression profiles of young adults with AMI to control subjects for the identification of proteins (candidate biomarkers) that are differentially expressed in AMI patients. This study also aimed to determine the plasma concentrations of the candidate biomarkers in young adults with normotension, prehypertension, hypertension and AMI and evaluate the relationship between AMI and potential CAD biomarker/s in young hypertensive and prehypertensive subjects. This study comprised of two phases; discovery and verification. In the discovery phase, proteins in the pooled plasma samples from young male adults (10 AMI patients and 10 controls) aged 18 to 45 years were separated by two-dimensional gel electrophoresis (2-DE). The protein spots that were differentially expressed in AMI patients relative to the controls were identified via matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry. In the verification phase, the plasma concentrations of the identified proteins were measured using enzyme-linked immunosorbent assay (ELISA) in 40 plasma samples of control, prehypertensive, hypertensive and AMI groups. In the discovery phase, haptoglobin (Hp), apolipoprotein AI (Apo AI) and apolipoprotein AIV (Apo IV) were significantly upregulated in AMI patients in comparison to the controls ($p < 0.05$). Meanwhile in the verification phase, the plasma concentration of Hp was significantly higher in AMI patients in comparison to the control, prehypertensive and hypertensive subjects (290.63±99.90 vs. 170.02±108.11 vs. 175.05±108.11 and vs. 208.47±112.97 ng/ml, $p < 0.006$) respectively. The plasma concentrations of Apo AI and Apo AIV were also elevated in AMI patients, yet the increases were not significant compared to the other groups ($p > 0.05$). Plasma concentration of Hp was significantly associated with young AMI (OR: 1.019, 95% CI: 1.006-1.033, $p = 0.003$) after adjusting for other known CAD risk factors. There was also a significant association between AMI and plasma concentration of Hp in hypertensive and prehypertensive subjects (OR: 0.985, 95% CI: 0.973-0.997, $p = 0.017$ and OR: 0.981, 95% CI: 0.969-0.993, $p = 0.002$) respectively, independent of other known CAD risk factors. Plasma Hp concentration was significantly correlated with high sensitivity C-reactive protein hs-CRP ($r = 0.370$, $p < 0.001$). In Conclusion, consistent upregulation of Hp in discovery and verification phases reflect its potential role as a biomarker of CAD in young adults. Hp is also a potential CAD biomarker that could be utilized as AMI predictor in young adults with hypertension and prehypertension. The significant correlation between Hp and hs-CRP indicates the potential role of these proteins as inflammatory markers in the establishment of CAD in young adults.

خلاصة البحث

فشل قلبي حاد هي المظاهر السريرية الأكثر شيوعا لمرض القلب التاجي . لم يعد السن مبكرا عاملا وقائيا حيث تزداد نسبة الإصابة بالشباب البالغين المصابين بـ فشل قلبي حاد. تم تحديد إرتفاع ضغط الدم كعامل خطر مهم في تطوير مرض القلب التاجي في سن مبكرة. يرتبط إرتفاع ضغط الدم دون إدارة مناسبة أيضًا بزيادة خطر الإصابة بـ مرض القلب التاجي. وبالتالي ، فإن تحديد العلامات البيولوجية مرض القلب التاجي في البالغين الصغار ارتفاع ضغط الدم وما قبل ارتفاع ضغط الدم ضروري لتحسين التنبؤ فشل قلبي حاد في هذه الأفواج. تم اقتراح التحليل البروتيني باعتباره أفضل طريقة في تحديد العلامات البيولوجية في الأمراض متعددة العوامل مثل مرض القلب التاجي. الهدف: كان الهدف الأول من هذه الدراسة هو مقارنة ملامح التعبير البروتين من الشباب البالغين مع فشل قلبي حاد للسيطرة على الموضوعات لتحديد العلامات البيولوجية المرشحة التي يتم التعبير عنها بشكل مختلف في المرضى فشل قلبي حاد. كان الهدف الثاني هو تحديد تركيزات البلازما الخاصة بالعلامات البيولوجية في البالغين الصغار المصابين بالضغط الطبيعي وارتفاع ضغط الدم وماقبل ارتفاع ضغط الدم و فشل قلبي حاد لتقييم العلاقة بين فشل قلبي حاد والعلامة البيولوجية مرض القلب التاجي المحتمل في موضوعات ارتفاع ضغط الدم وما قبل ارتفاع ضغط الدم. الطريقة: تتألف هذه الدراسة على مرحلتين: الاكتشاف والتحقق. في مرحلة الاكتشاف ، تم فصل البروتينات في عينات البلازما المجمعة من الشباب البالغين (١٠ مرضى فشل قلبي حاد و ١٠ عناصر تحكم) تتراوح أعمارهم بين ١٨ إلى ٤٥ عامًا بواسطة جهاز الفصل الكهربائي ثنائي الأبعاد. تم تحديد بقع البروتين التي بواسطة المصفوفة. في مرحلة التحقق ، تم قياس تركيزات البلازما للبروتينات المحددة باستخدام مقياس الإمتصاص المناعي في ٤٠ عينة من البلازما للتحكم ، ارتفاع ضغط الدم وماقبل ارتفاع ضغط الدم ، ومرضى فشل قلبي حاد. النتائج: في مرحلة الاكتشاف ، تم تنظيم هابتوغلوبي ، أبوليبوبروتين AI ، وأبوليبوبروتينAIV بشكل كبير في مرضى فشل قلبي حاد مقارنةً بعناصر التحكم (ع احتشاء فشل قلبي حاد هي المظاهر السريرية الأكثر شيوعا لمرض القلب التاجي). لم يعد السن مبكراً عاملاً تم التعبير عنها تفاضليًا في مرضى فشل قلبي حاد بالنسبة لعناصر التحكم من خلال قياس الطيف الكتلي للرياح / التأين بالليزر المدعم وقائياً حيث تزداد نسبة الإصابة بالشباب البالغين المصابين بـ فشل قلبي حاد. تم تحديد ارتفاع ضغط الدم كعامل خطر مهم في تطوير مرض القلب التاجي في سن مبكرة. يرتبط ارتفاع ضغط> ٠,٠٥. بينما في مرحلة التحقق ، كان تركيز البلازما لـ هابتوغلوبي أعلى بشكل ملحوظ في مرضى فشل قلبي حاد .مقارنةً بالمواضيع السابقة لارتفاع ضغط الدم وماقبل ارتفاع ضغط الدم (٢٩٠,٦٣.± ٩٩,٩٠ مقابل ١٧٥,٠٢± ١٠٨,١١ مقابل ١٧٥,٠٥ ± ١٠٨,١١ و مقابل ٢٠٨,٤٧± ١١٢,٩٧ng / مل ، ع <٠,٠٠٦) على التوالي. كانت تركيزات البلازما من أبوليبوبروتين AI و أبوليبوبروتين AIV مرتفعة أيضًا في مرضى فشل قلبي حاد ، لكن الزيادات لم تكن كبيرة مقارنة بالمجموعات الأخرى (ع =٠,٣٢ و ع = ٠,٩٥٧). ارتبط تركيز البلازما لـ هابتوغلوبي بشكل كبير مع فشل قلبي حاد الشاب (نسبة الارجحية: ١,٠١٩، مجال الثقة: ١,٠٠٦- ١,٠٣٣، ع = ٠,٠٠٣) بعد التعديل لعوامل الخطر المعروفة الأخرى لـ فشل قلبي حاد. كان هناك أيضًا ارتباط مهم بين فشل قلبي حاد وتركيز البلازما لـ هابتوغلوبي في موضوعات ارتفاع ضغط الدم وخافضة الضغط (نسبة الاجحية:٠,٩٨٥ ، ع = ٠,١٧، مجال الثقة : ٠,٩٧٣-٠,٩٩٧ ٩٥٪ ، ع = ٠,٠١٧ ونسبة الارجحية : ٠,٩٨١ ، مجال الثقة: ٠,٩٦٩ - ٠,٩٩ ٩٥٪ ، ع = ٠,٠٠٢) على التوالي ، مستقلة عن عوامل الخطر المعروفة الأخرى. ارتبط تركيز البلازما هابتوغلوبي بشكل كبير مع حساسية عالية من البروتين سي التفاعلي r =٠,٣٧٠ ،ع > ٠,٠٠١). الخلاصة: يعكس الانتظام المتسق لـ هابتوغلوبي في مراحل الاكتشاف والتحقق دورها المحتمل كمؤشر حيوي لتطوير مرض القلب التاجي في الشباب. تعد هابتوغلوبي أيضًا علامة بيولوجية مرض القلب التاجي محتملة يمكن استخدامها في تحديد البالغين المصابين بارتفاع ضغط الدم وماقبل ارتفاع ضغط الدم ، والذين يتعرضون لخطر كبير من الإصابة بتطوير مرض القلب التاجي. يشير الارتباط الهام بين هابتوغلوبي و البروتين سي التفاعلي إلى الدور الهام للمسارات الالتهابية في إنشاء مرض القلب التاجي عند البالغين الصغار.

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
Apo AI	Apolipoprotein AI
Apo AIV	Apolipoprotein AIV
APS	Ammonium persulfate
BMI	Body mass index
CAD	Coronary artery disease
CABG	Coronary artery bypass surgery
CI	Confidence interval
CK-MB	Creatinine kinase-myocardial band
CRF	Case record form
CTU	Clinical trial unit
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
1-DE	One-Dimensional electrophoresis
2-DE	Two-Dimensional electrophoresis
ECG	Electrocardiography
ELISA	Enzyme-linked immunosorbent assay
EDTA	Ethylenediaminetetraacetic acid
FBS	Fasting blood sugar
HCl	Hydrochloric acid
HDL	High density lipoprotein
Hs-CRP	High sensitivity C-reactive protein
Hs-cTn	High sensitivity cardiac troponin
HTAA	Hospital Tengku Ampuan Afzan
Hp	Haptoglobin
HRP	Horseradish Peroxidase
IEF	Iso electric focus

IPG	Immobolized pH gradient
iTRAQ	Isobaric tags for relative and absolute quantification
JNC	Joint National Committee
kDa	Kilodalton
LDL	Low density lipoprotein
mRNA	Messenger RNA
mmHg	Milimetre per mercury
MALDI TOF	Matrix-assisted laser desorption/ionization-time of flight
MOH	Ministry of Health
MS	Mass spectrometry
mM	Milimolar
ml	Mililitre
MREC	Medical Review and Ethics Committee
NCVD	National Cardiovascular Database
NMRR	National Medical Research Register
NHMS	National Health and Morbidity Survey
NSTEMI	Non-ST Elevated myocardial infarction
OD	Optical density
OR	Odd ratio
PCI	Percutenous coronary intervention
RR	Relative risk
SBP	Systolic blood pressure
SDS PAGE	Sodium dodecyl supfate polyacrylamide gel eletrophoresis
SMCs	Smooth muscle cells
STEMI	ST-elevated myocardial infarction
TC	Total cholesterol
TEMED	Tetramethylenediamine
USD	United State Dolar
vCAM-1	Vascular cell adhesion molecule 1
Vs.	Versus
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND AND JUSTIFICATION OF RESEARCH

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality that accounts for almost one third of deaths worldwide. In the United States, approximately 2200 Americans die of CVD each day, roughly one death in every 40 seconds (Mozaffarian, Benjamin, Go, Arnett, Blaha, Cushman, et al., 2016). The healthcare cost to manage CVD was about USD$ 272 billion (approximately RM 1132 billion) in 2010 and estimated to triple to USD$ 818 billion (approximately RM 3405 billion) in 2030 (Tran, Ohinmaa, Thanh, & Welsh, 2017). Unfortunately, nowadays CVD is not merely a disease in developed communities, but it has also affected developing countries. In fact, Southeast Asia was predicted to have the highest percentage increase in CVD-related deaths by 2030 (World Health Organization [WHO], 2017).

In Malaysia, CVD is the most common cause of death and accounted for 23% of total hospital mortality (Ministry of Health, 2015). The most prevalent CVD is coronary artery disease (CAD), specifically acute coronary syndrome (ACS) which includes acute myocardial infarction (AMI) and angina. The hospitalisation cost for AMI patient requiring percutaneous coronary intervention (PCI) is approximately RM 12,117 in public hospitals and RM 16,289 in teaching hospitals (Lee, Azman, Ahmad, Low, Liau, Anchah, et al., 2017). The economic burden due to AMI is expected to increase as the prevalence of AMI is shifting to younger Malaysian adults. The mean age of AMI patients in Malaysia is 58 years old (Wan Ahmad, 2017), about seven

years younger compared to AMI patients in general populations (Sorbets, Greenlaw, Ferrari, Ford, Fox, Michal, et al., 2017).

It is an established fact that an increasing age is a non modifiable risk factor for AMI (Agostino, Vasan, Pencina, Wolf, Cobain, Massaro, et al., 2008; Hajar, 2017). Unfortunately, young age is no longer protective as the incidence of AMI in young adults is currently increasing. Over the past four decades, there has been a decline in AMI admissions among the general population (Bhatnagar, Wickramasinghe, Wilkins, & Townsend, 2016). However, there has been no concomitant reduction in AMI admissions for patients below the age of 55 (Gupta, Wang, Spertus, Geda, Lorenze, Nkonde-Price, et al., 2014). The reported incidence of young patients diagnosed with AMI varied from 3% to 10% in high income populations, and 10% to 20% of total CAD admissions in low to middle income populations (Joshi, Islam, Pais, Reddy, Dorairaj, Kazmi, et al., 2007; Shah, Kelly, Cox, Wong, & Soon, 2016).

According to the Malaysia National Cardiovascular Disease Database (NCVD) Registry Report from 2007 to 2009, approximately 16% of the AMI patients who underwent PCI in tertiary hospitals were less than 45 years for male and 55 years for female (Zuhdi, Mariapun, Mohd Hairi, Wan Ahmad, Abidin, Undok, et al., 2013). A more recent NCVD-PCI Registry in 2016 reported the percentage of AMI patients aged less than 50 years old had increased from 22.1% between 2013 till 2014 to 23.7% between 2015 till 2016 (Wan Ahmad, 2017b). Meanwhile, NCVD-ACS Registry Report in 2016 documented that approximately 25% of ACS admissions from 2014 to 2015 were patients aged less than 50 years old (Wan Ahmad, 2017a). Apparently, AMI remains a principal cause of deaths among male Malaysian adults (13.2%) in the

past five years as reported by the Department of Statistics Malaysia in 2017 (Health Fact Ministry of Health, 2017)

The diagnosis of AMI at a prime age during family and career establishment, leads to significant adverse effects on the physical well-being and mental state of the patients, their families and the community. Furthermore, AMI at young age is more prevalent in males, who are usually the main breadwinners for the families. AMI at this productive age contributes to a greater socioeconomic impact due to the loss of vital human capital, increased family financial burden and excessive usage of public health care facilities. It has been reported that approximately 15% of young patients were not able to return to work following AMI episode due to deterioration of health condition that compromised their performances at the workplace (Dreyer, Xu, Zhang, Du, Strait, Bierlein, et al., 2016).

In the light of significant health and economic burden of AMI in young adults, identification of those with a higher risk of developing CAD at a young age is crucial to improving disease preventative strategies. Undeniably, the traditional risk factors such as hypercholesterolemia, hypertension, smoking, diabetes and family history have important role in identifying those at high risk of developing CAD. However, the risk of CAD in young adults is usually underestimated, as the young age is considered as a main protective factor (Agostino et al., 2008; Lakatta & Levy, 2003). Therefore, with the increasing trend in the prevalence of premature AMI, additional biomarkers are required to improve the risk stratifications of CAD among young adults.

Apart of smoking that is found to be the most prevalent risk factor for young adults with AMI in general population, hypertension remains an important risk factor

among young Malaysian AMI patients (Hoo, Foo, Mohd, & Lim, 2016; Zuhdi et al., 2013). Unlike smoking which is an obvious high-risk behaviour, hypertension particularly in young adult is more challenging to be recognized due to to lower level of health awareness in this age group (Abdul-razak, Daher, Ramli, Ariffin, Mazapuspavina, Ambiga, et al., 2016).

Consequently, young patient with the first episode of AMI was more likely to have untreated hypertension compared to the elderly AMI patients (OR: 2.99; 95% CI: 2.00-4.46, $p < 0.001$) (Chan, Woo, Wong, Chia, Sutandar & Tan, 2006). Poor management of high blood pressure (BP) may lead to acceleration of CAD development. It has been shown that uncontrolled hypertension in young adult was associated with higher relative risks (RR) for CVD mortality than older hypertensive patients; RR: 4.1, 95% CI 3.7-4.6, RR: 2.6, 95% CI 2.4-2.9 and RR: 1.9, 95% CI 1.8-2.0 at ages 35-59, 60-69 and 70-79 years respectively (Lewington, Lacey, Clarke, Guo, Kong, Yang, et al., 2016).

Besides hypertension, there is increasing evidence that individuals with prehypertension (BP 120-139/80-89 mm Hg) is almost twice as likely to develop CVD as normotensive individuals (Huang, Wang, Cai, Mai, Hu, Tang & Xu, 2013). The risk of CVD is higher in individuals with Stage 2 prehypertension (BP 130-139/85-89) than those in Stage 1 prehypertension (BP 120-129/80-84 mm Hg) (Huang et al., 2013). Therefore, accurate CVD risk assessement and effective blood pressure control are not only crucial at hypertension stage, individuals with prehypertension should also be identified and managed accordingly to reduce the risk of CVD development.

Current management for hypertension with low CVD risk and prehypertension is risk factor modification as recommended by the Malaysia 5th Edition of Clinical

Practice Guideline for Management of Hypertension (2018). Unfortunately, risk factor modification strategies seem less likely to benefit the young people due to a false sense of good health, which cause delays in seeking medical advice and poor compliance (Hulsegge, Looman, Daviglus, Schouw, & Verschuren, 2016). A survey performed among 3501 young AMI patients showed that only half of patients believed that they were at risk of heart disease prior to the acute event (Leifheit-Limson, D'Onofrio, Daneshvar, Geda, Nueno, Spertus & Krumholz, 2015). These patients also had never discussed risk factors modification with their health care providers, despite nearly all of them having more than one risk factor, and 64% having more than three risk factors.

Apparently, CAD risk among young hypertensive and prehypertensive adults are commonly ineffectively assessed. Thus, the role of biological markers in identifying young adults who are at risk of CAD in these cohorts has grown in importance. The identification of CAD biomarkers among young adults with elevated blood pressure will improve predictive accuracy of CAD and enhance clinical decision for blood pressure management in the low CVD risk group.

High-sensitivity C-reactive protein (hs-CRP) is one of the most promising protein markers in predicting the occurrence of CAD in a clinical setting (Torres & Ridker, 2003; Wang, Tan, Han, Bai, He & Liu, 2017). However, hs-CRP is a general inflammatory marker, thus it is less specific as it may be elevated in other inflammatory reactions. Consequently in CAD, the use of multi-biomarkers approach was proposed to produce a more accurate predictive value, instead of depending on a single biomarker (Bogavac-stanojevic & Jelic, 2010).

The emergence of ‘omic’ technologies such as genomic, proteomic and metabolomics have allowed more research opportunities in the discovery of new CAD biomarkers. Of these, proteomic analysis is proposed to be the best method to study multifactorial disease such as CAD, which is a result of interactions between genetic abnormalities and environmental influences (Singh, Aikawa, & Aikawa, 2016). Protein is the main functional component in any cell or tissue. Thus, modifications in protein expression at various stages of the disease development are potential candidates for risk, diagnostic or prognostic markers.

CAD is a silent disease and the development of underlying atherosclerosis occurs many years prior to the acute presentation of AMI. Several pathophysiological mechanisms such as inflammation, lipid dysregulation, oxidative stress and coagulation have been proposed to play important roles in the establishment of atherosclerotic plaques (Ambrose & Singh, 2015). Each process is associated with different proteins expressions. Hence, investigation on the alterations of protein expression in diseased tissues may reflect the pathophysiological changes that occur, and lead to the discovery of novel biomarkers as well as therapeutic target proteins.

Plasma proteomic study specific to young AMI patients is essential to discover potential CAD biomarkers that could improve the risk stratification, diagnosis, and prognostication of the disease in younger population. Apart from predicting CAD in healthy individuals, the new biomarker might be utilized as a predictor of CAD in young prehypertensive and hypertensive adults. Such discovery is important to improve clinical decision for blood pressure control in young adults. Additionally, plasma proteomic study specific to young adults may help unearth the reason behind the acceleration of atherosclerotic process which leads to the early emergence of AMI.