

UNIVERSITI PUTRA MALAYSIA

ROLE OF 18FLUORINE FLUORODEOXYGLUCOSE IN VULNERABLE PLAQUE DETECTION FOR IDENTIFYING HIGH RISK PATIENTS

SHAZREEN BINTI SHAHARUDDIN

FPSK(m) 2013 27



ROLE OF ¹⁸FLUORINE FLUORODEOXYGLUCOSE IN VULNERABLE PLAQUE DETECTION FOR IDENTIFYING HIGH RISK PATIENTS.

By

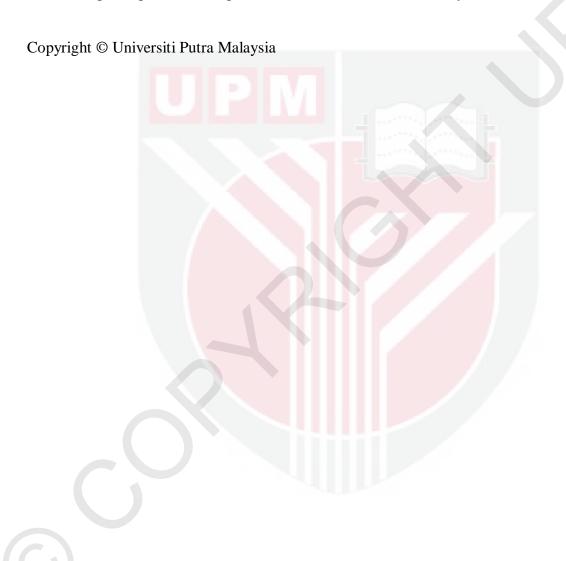
SHAZREEN BINTI SHAHARUDDIN

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

OCTOBER 2013

COPYRIGHT

All material contained within the thesis, including without limitation text, logos, icons, photographs and all other artwork, is copyright material of Universiti Putra Malaysia unless otherwise stated. Use may be made of any material contained within the thesis for non-commercial purposes from the copyright holder. Commercial use of material may only be made with the express, prior, written permission of Universiti Putra Malaysia.



Abstract of thesis presented to the Senate of University Putra Malaysia in fulfillment of the requirement for the degree Master of Science.

ROLE OF ¹⁸FLUORINE FLUORODEOXYGLUCOSE IN VULNERABLE PLAQUE DETECTION FOR IDENTIFYING HIGH RISK PATIENTS.

By

SHAZREEN SHAHARUDDIN

OCTOBER 2013

Main Supervisor: Prof. Abdul.Jalil Nordin, PhD

Faculty: Medicine and Health Science

FDG-PET/CT is a combined functional and structural multi modality imaging tool that can be utilized to detect atherosclerotic plaques. This study observed the prevalence of active and calcified plaques in selected arteries during whole-body 18F-FDG PET-CT and correlate the findings with risk factors in coronary artery disease. Beside that, the relationship of active and calcified plaque activity with inflammatory biomarker were determine from the blood marker. The record of 47 patients, which were divided into 17 patients retrospectively and 30 patient prospectively alongside serum inflammatory marker (eg.IL-6 and CRP) and cholesterol (eg lipid profile) undergone whole body FDG PET-CT study in various oncology cases were reviewed. To evaluate the cutoff value for abnormal uptake, retrospective study was conducted to identify patient at risk of developing vascular disease. Mean age was 58±10.3 years old. The presence of 18F-FDG uptake and calcification in selected vascular walls were evaluated. The composition of plaque were recorded using CT value in Housfield unit (HU max). The intensity of 18F-FDG uptake was measured as maximum blood-normalized standardize uptake value (SUVmax). 18F-FDG uptake (SUVmax) and calcification (HUmax) was significantly highest in the carotid walls

with (1.91±0.11) and (631.7±215.5) respectively. There was significant relationship between high BMI (overweight) with ¹⁸FDG uptake, while calcified artery significant related with hyperlipidemia, diabetes mellitus and hypertension. However the blood marker (such as C-reactive protein) showed significant with high ¹⁸FDG uptake and high calcified artery. Beside that, calcified artery showed there was no significant and direct correlation with inflamed vascular wall (SUVmax). This study showed that 18F-FDG PET-CT can be utilized in detecting focal high FDG uptake within vascular plaque in early recognition of high risk patients having coronary artery disease.

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

PENGGUNAAN ¹⁸FLUORINE FLUORODEOXYGLUCOSE PADA PLAK YANG TIDAK STABIL DALAM MENDETEKSI PESAKIT YANG BERISIKO TINGGI.

Oleh

SHAZREEN SHAHARUDDIN

OKTOBER 2013

Pengerusi: Prof. Abdul. Jalil Nordin, PhD

Fakulti: Perubatan dan Kesihatan.

FDG PET/CT adalah gabungan fungsi dan struktural multimodaliti alat pengimejan yang boleh digunakan untuk mengesan plak-plak aterosklerosis. Dalam kajian ini, kelaziman aktif dan pengapuran plak dalam arteri yang dipilih menggunakan 18F-FDG PET CT dikaitkan dengan hasil penemuan faktor risiko terjadinya penyakit vaskular. Selain daripada itu, hubungan diantara aktiviti plak mudah terjejas dengan inflamasi parameter dari penanda darah direkod . Terdapat 47 pesakit, yang dibahagikan kepada 17 pesakit retrospektif dan 30 pesakit prospektif berserta pengambilan serum darah (contohnya IL-6 dan CRP) dan kolesterol (contohnya profil lipid) dimana setiap pesakit menjalani scan pada seluruh badan menggunakan FDG PET/CT dalam pelbagai kes onkologi. Untuk evaluasi nilai purata bagi abnormal plak, kajian retrospektif telah dijalankan bagi mengidentifikasi pesakit yang berisiko untuk mendapat penyakit vaskular. Purata umur adalah 58±10.3 tahun. Pengambilan aktiviti 18F-FDG dan pengapuran pada dinding vaskular yang dipilih telah dinilai. Komposisi plak direkodkan menggunakan nilai CT dalam unit Housfield (HU max). Keamatan pengambilan aktiviti 18F-FDG telah disukat menggunakan unit 'Maximum blood-normalized standardize uptake value' (SUVmax), pengambilan aktiviti 18F-FDG (SUVmax) dan pengapuran (HUmax) menunjukkan nilai tertinggi dalam dinding karotid dengan purata (1.91±0.11) dan (631.7±215.5). Terdapat hubungan diantara BMI tinggi (melebihi paras normal) dengan pengambilan aktiviti FDG, sementara pengapuran arteri secara signifikasi berkait dengan hiperlipidemia, diabetes melitus dan hypertensi. Manakala, penanda darah (seperti protein C-reaktif) menunjukkan signifikasi dengan peningkatan pengambilan aktiviti FDG dan pengapuran arteri. Selain itu, pengapuran arteri menunjukkan tiada korelasi dengan inflamasi dinding arteri (SUVmax). Kesimpulannya menujukkan bahawa 18F-FDG PET CT boleh digunakan dalam mengesan peningkatan aktiviti FDG dalam plak vaskular bagi pencegahan supaya dapat mengurangkan risiko berlakunya penyakit arteri koronari.



AKNOWLEDGEMENT

First and foremost, I would like to thank and praise Allah the Almighty who has enabled me to conduct and successfully completed this study. Whatever is good this work contains is due to Allah blessings and whatever is bad contains is due to myself.

I would like to express my sincere gratitude to my supervisor, Prof. Dr Abdul Jalil Nordin for his supervision, generous support and guidance from initial to final accomplishment of this research. My warmest gratitude also goes to my co-supervisor Dr.Zaid Fattah Azman for his valuable time and insightful comments especially in helping me in the statistical analysis.

My deepest appreciation is also to my external co-supervisor Prof. Dr Khartiza Ali and Prof. Dr Abdul Latiff for their support and assist once during my field working. This gratitude also is to Dr. Fathinul Fikri for his support and helping me in collect data and sincere thanks to all staff of PPDN (Pusat Pengimejanan Diagnostic Nuclear) for their kind assistance.

Above all, I shall remain eternally grateful to my beloved parents, my father Prof. Dr Shaharuddin Mohd and my mother Prof. Dr. Rosnani Hashim who will always be my enormous source of inspiration and I dedicated all my effort and hard work to both of them. To my wonderful husband Mohd Firdaus Zulkafli ,my sister Shazwani Shaharuddin and my brother Muhammad Shazril Shaharuddin, thank you for your support.

Thank You Very Much.

SHAZREEN SHAHARUDDIN

2013

I certify that a Thesis Examination Committee has met on 3 Oktober 2013 to conduct the final examination of Shazreen Binti Shaharuddin on her thesis entitled "Role of ¹⁸Fluorine Fluorodeoxyglucose in vulnerable plaque detection for identifying high risk patients "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.

Members of the Thesis Examination Committee were as follows:

M. Iqbal bin Saripan, PhD

Associate Professor Faculty of Engineering University Putra Malaysia (Chairman)

Norhafizah binti Mohtarrudin, PhD

Senior Lecturer
Faculty of Medicine and Health Sciences
University Putra Malaysia
(Internal Examiner)

Rozi binti Mahmud, PhD

Professor
Faculty of Medicine and Health Sciences
University Putra Malaysia
(Internal Examiner)

Sazilah Ahmad Sarji, PhD

Professor, Datin University Malaya Malaysia (External Examiner)

NORITAH OMAR, PhD

Associate Professor and Deputy Dean School of Graduate Studies Universiti Putra Malaysia This thesis submitted to the Senate of University Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of master of science. The members of the Supervisory Committee were as follows:

Abdul Jalil bin Nordin, PhD

Professor Faculty of Medicine and Health Sciences University Putra Malaysia (Chairperson)

Ahmad Zaid Fattah bin Azman

Senior Lecturer
Faculty of Medicine and Health Sciences
University Putra Malaysia
(Members)

Khatiza Haida Ali, PhD

Professor
Faculty of Medicine and Health Sciences
University Putra Malaysia
(Members)

Abdul Latiff bin Mohamed, PhD

Professor Cyberjaya University College of Medicine Sciences Malaysia (Members)

BUJANG BIN KIM HUAT,PhD

Professor and Dean School of Graduate Studies, Universiti Putra Malaysia.

Date: 20 January 2014

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or any other institution.

SHAZREEN BT SHAHARUDDIN

Date: 3 Oktober 2013

TABLE OF CONTENTS

ABSTRACT ABSTRAK ACKNOWLEDGEMENTS APPROVAL DECLARATION LIST OF TABLES LIST OF FIGURES LIST OF ABBREVIATIONS	Page ii iv vi vii-viii ix xv xvi xiii
CHAPTER I: INTRODUCTION	1
1.1 Background	1-4
1.2 Pathogenesis Of Atheroslcerosis	5-7
1.3 Atherosclerosis Risk Factors	
(a) Major risk factors	
1.3.1 Non modifiable 1.3.1.1 Age 1.3.1.2 Gender	8
1.3.2 Modifiable 1.3.2.1 Hypertension 1.3.2.2 Diabetes mellitus 1.3.2.3 Hyperlipidemia 1.3.2.4 Smoking	9 9 10 11
(b) Minor risk factors	
1.3.1 Obesity	12
1.4 Clinical Use Of Atherosclerotic Risk Factors	13-14
1.5 Clinical Detection Of Atherosclerotic Disease	
1.5.1 CT 1.5.2 MRI 1.5.3 PET 1.5.4 PET/CT	15 16 18 20
1.6 Problem Statement	23

1.7 Research Questions	23
1.8 Significance Of The Study	24
1.9 Research Hypothesis	24
1.10 Objective Of The Study	
1.10.1 General Objectives1.10.2 Specific Objectives	25 25
CHAPTER II: LITERATURE REVIEW	26
2.1 Background	26-27
2.2 Risk Factors	
a) Major risk factors	27
2.2.1 Non-Modifiable	
2.2.1.1 Age 2.2.1.2 Gender	28 28-29
2.2.2 Modifiable	
2.2.2.1 Hypertension 2.2.2.2 Diabetes mellitus	29
2.2.2.3 Hyperlipidemia	30 31
2.2.2.4 Smoking	32
b) Minor risk factors	
2.2.1 Obesity	33
2.3 Serum Markers	
2.3.1 C-Reactive Protein	34
2.3.2 Interleukin-6	35
2.3.3 Lipid	36
2.4 Imaging Modality In Detecting Plaque In Vascular Wall.	36-38
CHAPTER III: METHODOLOGY	39
3.1 Background	39

3.2 Study Duration	40
3.3 Ethic	40
3.4 Study Population	
3.4.1 Retrospective group	40
3.4.2 Prospective group	41
3.5 Sample Size	
3.5.1 Calculation Of Sample Size	42
3.6 Sampling Population	
3.6.1 Inclusion Criteria	42
3.6.2 Exclusion Criteria	43
3.7 Data Collection	
3.7.1 Patients history	43
3.7.2 Blood parameter	43-49
3.8 PET/CT Study And Data Analysis	
3.8.1 Patient Preparation.	49-50
3.8.2 Imaging Pet/Ct Technique	51
3.9 Image Analysis	52-58
3.10 Statistical Analysis	59
CHAPTER IV: RESULT	60
4.1. Study Demographic	C1
4.1.1 Non-modifiable risk factors characteristics 4.1.2 Modifiable risk factors characteristics	61 63
4.1.2 Modifiable fisk factors characteristics	03
4.2 Correlation Between Major Risk Factors And Plaque Characteristic On 18 F FDG PETCT	
4.2.1 Non Modifiable	65
4.2.2 Modifiable	67
	0,
4.3 The Relationship Of Fdg Uptake (SUV) And Plaque Hardening (HU)	
In Various Vessels.	69
4.4. The Correlation Between Blood Parameter (Atherosclerotic Risks),	
Semi Quantification Value (SUV) And Evidence Of Hardening Plaque	7.1
(Hu).	71

4.5. The Correlation Between Semi Quantification Value (SUV) And Evidence Of Hardening Plaque(HU)	
	73
4.6 Estimating A Suitable Cutoff Point For Maximum Standardized Uptake Value(SUV).	74-78
CHAPTER V: DISCUSSION	79
5.1 Sociodemographic	
(a) Major risk factors	
5.1.1 Non-modifiable 5.1.2 Modifibale	80 81-82
5.2. The Relationship Between SUV max and HUmax with Cardiovascular Risk Factors	
(a) Major risk factors	
5.2.1 Non-Modifiable	82-83
5.2.2 Modifiable	83-85
5.3 The Relationship Of FDG Uptake(SUV) And Calcification (HU) In Various Vessels	86
5.4 The Correlation Between Blood Parameter (Atherosclrotic Risks), Semi Quantification Value (SUV) And Evidence Of Hardening Plaque(HU)	
5.4.1 C-Reactive Protein (CRP) & Interleukin-6 (IL-6).	87
5.4.2 Lipid Profile	88
5.5 The Correlation Between Semi Quantification Value (SUV) And	
Evidence Of Hardening Plaque (HU).	89
5.6 Estimating A Suitable Cutoff Point For Maximum Standardized Uptake Value(SUV).	90
CHAPTER VI: SUMMARY, CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH	91
6.1 Study Conclusion	92-94
6.2 Limitations Of Study	94-95
6.3 Recommendations for future research	95

REFERENCES	96-111
APPENDICES	112-115
BIODATA OF THE AUTHOR	116
LIST OF PUBLICATION	117

