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

SHAZREEN BINTI SHAHARUDDIN

FPSK(m) 2013 27
ROLE OF \(^{18}\)FLUORINE 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.

Copyright © 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 $^{18}$FLUORINE 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 $^{18}$F-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 $^{18}$F-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 $^{18}$F-FDG uptake was measured as maximum blood-normalized standardize uptake value (SUVmax). $^{18}$F-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 $^{18}$FDG 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 $^{18}$FDG 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.

PENGUNGANAN \(^{18}\)FLUORINE 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 \(^{18}\)F-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 \(^{18}\)F-FDG dan pengapuran pada dinding vaskular yang dipilih telah dinilai. Komposisi plak direkodkan menggunakan nilai CT dalam unit Housfield (HU max). Keamatan pengambilan aktiviti \(^{18}\)F-FDG telah disukat menggunakan unit ‘Maximum blood-normalized standardize uptake value’ (SUVmax). Pengambilan aktiviti \(^{18}\)F-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 menunjukkan 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.
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 $^{18}$Fluorine 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
# CHAPTER I: INTRODUCTION

1.1 Background 1-4

1.2 Pathogenesis Of Atherosclerosis 5-7

1.3 Atherosclerosis Risk Factors

(a) Major risk factors

1.3.1 Non modifiable
   1.3.1.1 Age 8
   1.3.1.2 Gender 8

1.3.2 Modifiable
   1.3.2.1 Hypertension 9
   1.3.2.2 Diabetes mellitus 9
   1.3.2.3 Hyperlipidemia 10
   1.3.2.4 Smoking 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 15
   1.5.2 MRI 16
   1.5.3 PET 18
   1.5.4 PET/CT 20

1.6 Problem Statement 23
1.7 Research Questions

1.8 Significance Of The Study

1.9 Research Hypothesis

1.10 Objective Of The Study

   1.10.1 General Objectives
   1.10.2 Specific Objectives

CHAPTER II: LITERATURE REVIEW

2.1 Background

2.2 Risk Factors

   a) Major risk factors

      2.2.1 Non-Modifiable
         2.2.1.1 Age
         2.2.1.2 Gender

      2.2.2 Modifiable
         2.2.2.1 Hypertension
         2.2.2.2 Diabetes mellitus
         2.2.2.3 Hyperlipidemia
         2.2.2.4 Smoking

   b) Minor risk factors

      2.2.1 Obesity

2.3 Serum Markers

   2.3.1 C-Reactive Protein
   2.3.2 Interleukin-6
   2.3.3 Lipid

2.4 Imaging Modality In Detecting Plaque In Vascular Wall.

CHAPTER III: METHODOLOGY

3.1 Background
3.2 Study Duration

3.3 Ethic

3.4 Study Population
   3.4.1 Retrospective group
   3.4.2 Prospective group

3.5 Sample Size
   3.5.1 Calculation Of Sample Size

3.6 Sampling Population
   3.6.1 Inclusion Criteria
   3.6.2 Exclusion Criteria

3.7 Data Collection
   3.7.1 Patients history
   3.7.2 Blood parameter

3.8 PET/CT Study And Data Analysis
   3.8.1 Patient Preparation.
   3.8.2 Imaging Pet/Ct Technique

3.9 Image Analysis

3.10 Statistical Analysis

CHAPTER IV: RESULT

4.1. Study Demographic
   4.1.1 Non-modifiable risk factors characteristics
   4.1.2 Modifiable risk factors characteristics

4.2 Correlation Between Major Risk Factors And Plaque Characteristic On
   $^{18}$F FDG PETCT
   4.2.1 Non Modifiable
   4.2.2 Modifiable

4.3 The Relationship Of Fdg Uptake (SUV) And Plaque Hardening (HU)
   In Various Vessels.

4.4. The Correlation Between Blood Parameter (Atherosclerotic Risks),
   Semi Quantification Value (SUV) And Evidence Of Hardening Plaque
   (Hu).
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 80
   5.1.2 Modifiable 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