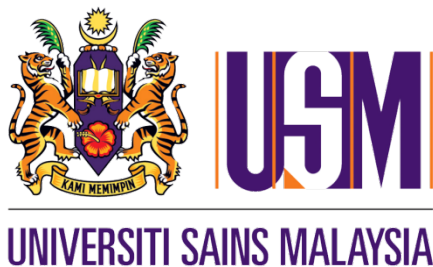


**ASSOCIATION BETWEEN ANKLE-BRACHIAL SYSTOLIC INDEX, PULSE  
OXIMETRY GRADIENT INDEX AND CT ANGIOGRAM OF LOWER LIMB  
AMONG TYPE 2 DIABETIC FOR DETECTING PERIPHERAL ARTERIAL  
DISEASE.**

**By:**

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**Dissertation Submitted in Partial Fulfillment of the Requirements for Master of  
Medicine (Radiology)**



**UNIVERSITI SAINS MALAYSIA**

2017

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## **LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS**

DM	Diabetes Mellitus
ECQ	Edinburgh Claudication questionnaire
PO	Pulse oximetry
ABSI	Ankle-brachial systolic index
CTA LL	Computed tomographic angiogram of lower limbs
HUSM	Hospital Universiti Sains Malaysia.
HbA1c	Hemoglobin A1c

## **ABSTRAK**

**Latar belakang:** Penyumbatan salur darah kaki adalah penyakit di kalangan pesakit diabetes mellitus jenis 2. Kebanyakan klinik kesihatan kurang mengambil berat tentang susur alur perawatan penyumbatan salur kaki ini. Justeru, dengan kajian ini kami buktikan keberkesanan alat-alat mudah di klinik sebagai satu cara mengesan penyakit ini dengan lebih awal, seterusnya membandingkan alat tersebut dengan imbasan CT salur darah kaki yang dijalankan di kalangan pesakit di Kubang Kerian, Kelantan.

**Objektif:** Untuk menentukan hubungkait antara perbezaan bacaan sistoli kaki dan tangan, perbezaan perfusi jari dan kaki dan CT angiogram kedua belah kaki bagi mengesan penyakit penyumbatan salur darah kedua belah kaki.

**Metodologi:** Pesakit yang telah datang membuat pemeriksaan di Klinik Pakar Diabetik, Hospital USM, Kelantan, Malaysia adalah layak dalam kajian. Pesakit dewasa, pengidap diabetes jenis ke-2, kandungan darah HbA1c lebih dari 6.5 peratus dalam masa 3 bulan telah diterima masuk dalam kajian. Simtom klaudikasi kaki telah di soal selidik melalui ECQ. Perfusi kedua belah pesakit di kenal pasti menggunakan perbezaan bacaan sistoli kaki dan tangan dan perbezaan perfusi jari dan kaki. CT angiogram kedua belah kaki dijalankan selepas itu. Keputusan kemudian diteliti.

**Keputusan:** Sebanyak 22 bilangan kaki dianalisa dari 11 orang pesakit. Hubungkait yang baik didapati antara perbezaan bacaan sistoli kaki dan sejarah klaudikasi kaki ( $r = 0.378$ ,  $p = 0.076$ ). Hubungkait yang sangat baik juga didapati antara perbezaan bacaan sistoli kaki dan perbezaan perfusi jari dan kaki ( $r = 0.818$ ,  $p = <0.001$ ) dalam kalangan pesakit. Didapati hubungkait penyumbatan salur darah kedua belah kaki dan perbezaan kedua bacaan sistoli dan perfusi jari dan kaki adalah signifikan dalam regresi logistic univariat ( $p = 0.016$ ). Kebarangkalian mendapat bacaan perbezaan bacaan sistoli dan perfusi jari

dan kaki yang abnormal adalah 12 kali lebih tinggi didapati dalam kes penyumbatan salur darah kaki yang teruk berbanding penyumbatan salur darah yang sederhana (ORc ,95% CI). Kebarangkalian mendapat bacaan abnormal perbezaan sistoli serta perfusi kedua jari dan kaki adalah 8 kali lebih tinggi di kalangan penyumbatan kaki yang teruk dibawah lutut berbanding pesakit yang mempunyai penyumbatan salur darah kaki yang sederhana ( $p = 0.037$ ).

**Kesimpulan:** Pesakit yang mempunyai penyumbatan salur darah di bawah lutut yang teruk mempunyai hubungkait yang sangat kuat dengan bacaan abnormal perbezaan sistoli dan perfusi jari dan kaki. Kajian ini membuktikan bacaan perbezaan perfusi jari dan kaki sama keberkesanannya dengan perbezaan bacaan sistoli tangan dan kaki bagi memberi diagnosis clinical penyumbatan salur darah kedua belah kaki dikenalpasti melalui CT angiogram.

**Kata kunci:** *Diabetes Mellitus jenis 2, perbezaan bacaan sistoli kaki dan tangan, perbezaan perfusi jari dan kaki, CT angiogram kedua belah kaki, penyumbatan salur darah kaki.*

## **ABSTRACT**

**Background:** Peripheral arterial disease (PAD) is a known macrovascular complication of type 2 diabetes. Most primary care clinic has no establish algorithm on how to screen patient with PAD. Hereby, we conducted a study among patient in tertiary hospital diabetic unit, by using simple useful, handy test and correlate the tests with diagnostic imaging to detect PAD in our local community in Kubang Kerian, Kelantan.

**Objective:** To determine association between ankle-brachial systolic index, pulse oximetry and CTA lower limb for detecting peripheral arterial disease among Type 2 Diabetic patients.

**Methodology:** Patients who attended Diabetic Specialist Clinic HUSM were eligible for the study. Adult patients with Type 2 DM has HbA1c more than 6.5% in 3 months were recruited. Symptoms of claudication were assessed using ECQ. The lower limb perfusion was evaluated by ABSI and PO gradient. Radiologically the perfusion was assessed using CTA LL as a gold standard. The severity of stenosis was categorized into <50% (minimal to mild stenosis) and  $\geq 50\%$  (moderate to severe stenosis). The site of stenosis (above and below knee) were also analysed.

**Results:** A total of 22 limbs from 11 patients were analysed. A strong association between abnormal ABSI and LPO gradient ( $r = 0.818$ ,  $p = <0.001$ ) in this study was obtained. There is significant fair association between ABSI findings and history of lower limb claudication ( $r = 0.378$ ,  $p = 0.076$ ) between patients. There was statistically significant association between present of stenosis and abnormal ABSI or PO gradient ( $p = 0.016$ ). On further analysis, the odd of having abnormal ABSI or PO gradient value is 12 times higher in patient with moderate to severe stenosis than those with minimal to mild arterial PAD (ORc ,95% CI). In single logistic regression, the odd of having abnormal ABSI or PO gradient value is 8 times higher in patient with moderate to severe below knee arterial



stenosis ( $\geq 50\%$  stenosis) than those with minimal to mild ( $<50\%$ ) above and below knee PAD ( $p = 0.037$ ). **Conclusions:** Patients who have severe below knee PAD has shown strong association with abnormal ABSI and PO. PO gradient has significant association with PAD as equal as ABSI and the result was confirmed by CTA LL study.

**Keywords:** *Type 2 Diabetes Mellitus, Peripheral arterial disease, Pulse Oximetry, Ankle brachial systolic index, Computed tomography of arterial lower limb.*

# CHAPTER 1: INTRODUCTION

## **1.1 Introduction.**

Peripheral arterial disease (PAD) is manifested as presence of atherosclerotic plaque within diseased lower extremities arteries. PAD is a macrovascular complication of type 2 diabetes mellitus. Framingham Heart study mentioned that only 20% of symptomatic PAD patient had diabetes. The figure does not include the asymptomatic patient which likely more than predicted. Study showed, at least one-half is asymptomatic, one-third have claudication and others are categorized as worse PAD (1).

Clinical tests are important to determine the next diagnostic and management steps. To the best of our knowledge, there was no clinical study performed regarding the association of ankle brachial systolic index and pulse oximeter gradient for PAD screening in Malaysia particularly in Kota Bharu, Kelantan populations. The purpose of this study is to determine association between the ankle brachial systolic index, pulse oximetry and CT angiography of lower limb (CTA LL) among Type 2 diabetic patient suffering from early PAD.

Peripheral arterial disease is one of the commonest circulatory problem. Mainly, in PAD the arteries are narrowed causing declining blood flow to patient's limbs. Risk factors attribute to peripheral arterial disease is atherosclerotic plaque of fatty deposition within the mural lining of the vessel. Deprivation of blood supply or perfusion occurred not only to the limbs but brain, kidneys and the coronary artery of the heart. Lower limbs could not cope with the lesser supply to keep the demands of tissue during walking which contributes to symptom of claudication. Biologically, in diabetes, proatherogenic formation may include vascular inflammation and derangements in cellular components of vasculature, alteration in blood cells and hemostatic factors.

Clinical tool to screen PAD symptoms and signs should be simplest, reproducible, handy and available in most general medical clinic. One of the tool is the noninvasive

method of measuring the ankle brachial systolic index using automated or manual sphygmomanometry instrument. The pulse oximetry also plays the best role to evaluate gradient oxygen saturation or perfusion of peripheral finger or toes.

Ankle brachial systolic index (ABSI) is a ratio between the ankle systolic peak pressure with brachial systolic peak pressure. ABSI is the best tool to detect asymptomatic PAD among population (2). This clinical test is simple, inexpensive, painless, reproducible and easily performed (3). An ABSI less than 0.90 diagnosed as significant lower limb PAD of more than 50% stenosis (sensitivity of 79%, specificity 96%) (4). By using ABSI as a clinical tool, the prevalence of PAD among diabetic type 2 patient is 14.4% in man and 14.9% among woman (5). The article mentioned, 28% of PAD may have risk of coronary artery disease. Other major risk factors also assessed in this study including the age, duration of diabetes, smoking history, HbA1c markers and blood pressure.

There are several articles using handy Pulse Oximetry (PO) as a tool for detection of peripheral skin saturation gradient between finger tips and toe among PAD patient. PO reflects the level of affected sites by simply applying on the finger and toes (6). According to Javier Ena et al, a finger-to-toe SaO<sub>2</sub> gradient more than 2% reading is considered diseased. In their study, they compared the ABSI and pulse oximeter finger-to-toe SaO<sub>2</sub> gradient, which is easier, faster and practical. If the signal are not able to obtained due to gangrenous or amputation, the next toe's signal is used (3). Javier Ena, et al mentioned that the sensitivity of the pulse oximetry greater than 2% show 42.6% and specificity of 79%, PPV 35.7%, NPV 83%, PLR 2.03 and NLR 0.73 which were statistically significant.

Javier Ena et al, recruited 250 samples who screened for claudication using ECQ and then underwent PO test and followed by ABSI. Each normal and abnormal reading

were determined. The result showed abnormal reading of PO ( $>2\%$ ) is 25.1% from the study, ABSI  $<0.9$  was 35.7% and ABSI of 0.9 -1.4 was 64.3%. Normal PO ( $\leq 2\%$ ) accounted 74.9%, ABSI  $<0.9$  is 16.2% and ABSI of 0.9 -1.4 is 81.4%. All of these results were statistically significant. From this study, we would like to reproduce the study and correlate the findings with CT angiography of lower limb.

CT angiography of the lower limb (7) provide information of the stenosed artery as well as better delineation of surrounding structure in pre and post operative procedure. Ultrasonography, MR angiography and digital subtraction angiography are the other useful tools to provide the information, however in this study we focused on CT angiogram scan as the gold standard study. However, the choice for imaging is depending on the background of the patient's comorbidity, availability of imaging tools, trained technologist and interest of the radiologist in particular centers (8). High spatial resolution and relatively non operator dependence has made CTA as our choice of diagnostic tool. Mostly some study except one, reported good summation of sensitivity and specificity by using CTA rather than digital subtraction angiogram in detecting hemodynamically relevant steno-occlusive lesions using four-channel CT (9). This means CTA has higher sensitivity and specificity for arterial occlusions rather than detection of stenosis.

For those patients whom revascularisation is considered and anatomical localization of stenoses or occlusion is important, an evaluation with duplex ultrasound or a magnetic resonance angiogram (MRA) may be valuable. Duplex ultrasound can directly visualise vessels and is also useful in the surveillance of post procedure patients for graft and stent patency. However, it is an operator dependent and accuracy may be difference form person to person. Contrast MRA is noninvasive with risk of renal insult which most of our patients have with preexisting Diabetes Mellitus. According to study, non-ionic iodine based contrast media are less harmful for kidney as compare to

gadopentate contrast media used in MRI study. While, the gold standard for vascular imaging is digital subtraction angiography (DSA), it is indicated primarily for anatomical evaluation of the patient in whom a revascularisation procedure is intended. Because it is an invasive test with small risk of contrast-induced nephrotoxicity “exploratory” angiography should not be performed for diagnosing PAD.

CTA LL is performed as a benefit for patient’s earliest detection of peripheral arterial disease. Though, there is a risk of radiation in CTA LL, the benefit is outweigh the risk. Apart from radiation to patient during CTA LL, there is no risk of radiation to patient’s family/ spouse or population after completing the scan.

PAD in earlier stage without imminent limb ischemia could prevent patient progress into severe complication. This study is also as the tool to help and educate patient on the initial symptom and sign of PAD as well as improve their quality of life.

## CHAPTER 2: OBJECTIVES OF STUDY

## **2.1 General objective:**

To determine association of ABSI, LPO gradient and CTA lower limb in diagnosing peripheral arterial disease among Type 2 DM patient.

## **2.2 Specific objectives:**

- 1) To determine association between claudication history and ankle brachial systolic index in type 2 DM
- 2) To determine association between peripheral oxygen saturation gradient and ankle brachial systolic index in type 2 DM
- 3) To determine association between peripheral oxygen saturation gradient and ankle brachial systolic index with degree of arterial occlusion using CTA LL.



## CHAPTER 3: MANUSCRIPT

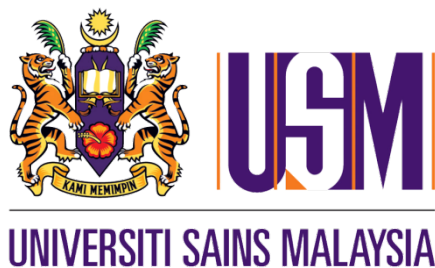
**3.1 Title page:**

**ASSOCIATION BETWEEN ANKLE-BRACHIAL SYSTOLIC INDEX, PULSE  
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### **3.2 Abstract**

**Background:** Peripheral arterial disease (PAD) is a known macrovascular complication of type 2 diabetes. Most primary care clinic has no establish algorithm on how to screen patient with PAD. Hereby, we conducted a study among patient in tertiary hospital diabetic unit, by using simple useful, handy test and correlate the tests with diagnostic imaging to detect PAD in our local community in Kubang Kerian, Kelantan.

**Objective:** To determine association between ankle-brachial systolic index, pulse oximetry and CTA lower limb for detecting peripheral arterial disease among Type 2 Diabetic patients.

**Methodology:** Patients who attended Diabetic Specialist Clinic HUSM were eligible for the study. Adult patients with Type 2 DM has HbA1c more than 6.5% in 3 months were recruited. Symptoms of claudication were assessed using ECQ. The lower limb perfusion was evaluated by ABSI and PO gradient. Radiologically the perfusion was assessed using CTA LL as a gold standard. The severity of stenosis was categorized into <50% (minimal to mild stenosis) and  $\geq 50\%$  (moderate to severe stenosis). The site of stenosis (above and below knee) were also analysed.

**Results:** A total of 22 limbs from 11 patients were analysed. A strong association between abnormal ABSI and LPO gradient ( $r = 0.818, p = <0.001$ ) in this study was obtained. There is significant fair association between ABSI findings and history of lower limb claudication ( $r = 0.378, p = 0.076$ ) between patients. There was statistically significant association between present of stenosis and abnormal ABSI or PO gradient ( $p = 0.016$ ). On further analysis, the odd of having abnormal ABSI or PO gradient value is 12 times higher in patient with moderate to severe stenosis than those with minimal to mild arterial stenosis (ORc ,95% CI). In single logistic regression, the odd of having abnormal ABSI or PO gradient value is 8 times higher in patient with moderate to severe below knee arterial PAD ( $\geq 50\%$  stenosis) than those with minimal to mild (<50%) above and below knee PAD ( $p = 0.037$ ).

**Conclusions:** Patients who have severe below knee PAD has shown strong association with abnormal ABSI and PO. PO gradient has significant association with PAD as equal as ABSI and the result was confirmed by CTA LL study.

**Keywords:** *Type 2 Diabetes Mellitus, Peripheral arterial disease, Pulse Oximetry, Ankle brachial systolic index, Computed tomography of arterial lower limb.*

### **3.3 Introduction**

Type 2 Diabetes Mellitus is the most common endocrine disease, rapidly rising as global health care problems and is threatening to reach pandemic level by 2030 (10). Macrovascular complication particularly peripheral arterial disease is manifested by atherosclerotic plaque, are among the devastating outcome especially in long standing type 2 DM patient (11). Discovery of intermittent claudication or distal trophic ulcer are one of the clinical manifestation (two third of patient), but at least one third of patients are asymptomatic (1).

Peripheral arterial disease (PAD) is one of the commonest circulatory problem among diabetic patients. In PAD, the arteries are narrowed causing declining blood flow to patient's limbs which contributes by atherosclerotic plaque of fatty deposition within the mural lining of the vessel. This may reduce the blood supply not only to the limbs but brain, kidneys and the coronary artery of the heart. Biologically, in diabetes, proatherogenic formation may include vascular inflammation and derangements in cellular components of vasculature, alteration in blood cells and hemostatic factors (12). The limbs could not cope with low perfusion to keep the demands, causing symptom of leg claudication during walking. Limb or toes gangrenous is the late sign of blood supply inadequacy which leads to sepsis and amputation.

Lack of emphasis or acknowledgement of PAD early assessment in clinical setting is the main problem nowadays. Majority of patients were unaware of a simple calf pain or claudication until the sign or symptom is too late. Here, our study is mainly to reinforce utilization of simple clinical tests, provide performance evidence of the tests, thus promote early PAD detection for better outcome. This study is also as the tool to help and educate patient on the initial symptom and sign of PAD as well as improve their quality of life. As far as our knowledge, there was no local study discussed on the association of ankle brachial systolic

index (ABSI) and pulse oximeter (PO) gradient for PAD screening in Malaysia particularly in Kota Bharu, Kelantan populations.

ABSI is the best tool to detect asymptomatic PAD among population (2) by using automated or manual sphygmomanometry instrument. Less than 0.9 ABSI signify more than 50% occlusion on angiogram with high specificity and sensitivity (4). The prevalence of PAD among type 2 DM patients are 14.4% in man and 14.9% in woman (5). Although, ABSI is considered standard method for diagnosis of PAD including in epidemiological field, laboratories of vascular study, clinical practice, this procedure need dedicated device, time consuming and required dedicated skills. These factors may explain the shortcoming on why PAD remains largely underdiagnosed particularly in general practice. Therefore, here we include the other test study, aimed for similar indication, which is PO whereby it is easily available in clinical practice and more practicable. At the end of our study, both tests were compare on the association in detecting PAD.

The pulse oximetry has been developed as non invasive screening method to detect low oxygen hemoglobin saturation in finger and toe tips. The rationale for using fingertip PO as screening for PAD is based on hypothesis that there would be a gradient oxygen saturation between upper and lower limbs in patients with significant perfusion defects. The assessment of pulse oximetry (PO) finger-to-toe saturation gradient decrease more than 2% reflects significant PAD (3, 6). Previous article (13), recruited 250 samples having claudication using Edinburgh claudication questionnaire (ECQ), underwent PO test followed by ankle-brachial systolic index (ABSI). This study concluded PO showed high sensitivity screening method for detecting PAD in patients with type 2 DM.

Computed tomography angiogram of lower limb were performed in this study as the validity test or gold standard study. This non-invasive imaging provides degree of arterial occlusion in better anatomical delineation. High spatial resolution, multidetector CT scan and

relatively non operator dependence has made CTA LL as our choice of diagnostic tool. Most of the study except one, reported good summation of sensitivity and specificity by using CTA rather than digital subtraction angiogram in detecting hemodynamically relevant stenocclusive lesions using four-channel CT (9). Although inferior to conventional catheter angiography, CTA can assess arteries as small as 1 mm in diameter. Because it is volumetric, CT angiography allows three-dimensional visualization of the vasculature to separate superimposed structures. CT scan can image small, tortuous coronary arteries as well as the renal (14) and neurovascular circulation (15, 16), up to and including a comprehensive evaluation of the aorta (17).

The purpose of this study is to determine association between the ABSI, PO and CT angiography of lower limb (CTA LL) among type 2 diabetic patients for detecting PAD. The objectives of our study are to determine association between claudication history and ABSI in type 2 DM, the association between PO gradient and ABSI, and determine association between PO gradient and ABSI with degree of arterial occlusion using CTA LL.

### **3.4 Materials and method**

#### **3.4.1 Study Population**

All patients with type 2 DM (based on WHO standard criteria) attended Diabetic Specialist Clinic Hospital USM were eligible for the study. This study was a collaborative study between Internal Medicine and Radiology Department, Hospital USM. Those who were 18 years and above and has HbA1c of more than 6.5% in 3 months presented with claudication were enrolled. Pregnant lady, Type 1 DM, contraindicated for ABSI measurement (such as mobility obese, large trophic ulcer), history of revascularization and lower limb instrumentation, GFR less than 30ml/min and absolute contraindicated to contrast media (severe anaphylactic/anaphylactoid reaction previously) were excluded. Patient was screened and assessed for symptomatic PAD using ECQ. Data collection started from January 2016 till October 2016.

#### **3.4.2 Data collection**

Demographic data and ECQ were taken and performed. Data includes age, gender, duration of diabetes mellitus since diagnosis, waist circumference and smoking habits were obtained. Biochemical data was included such as HbA1c, LDL, HDL, creatinine.

#### **3.4.3 Tools and index measurements:**

All patients underwent ABSI and PO tests. Pulse oximeter applied on fingers and toes tip (thumb and big toe) with 2 readings and the higher reading was chosen. The data was obtained and calculated. If the signal were not able to obtained due to gangrenous, the next toe's signal was used (3). PO of toes decrease of more than 2% (>2%) in arterial saturation from the finger tip is considered abnormal. (eg: toe SaO<sub>2</sub> 90%, Finger tip SaO<sub>2</sub> 95% =  $5/95 \times 100 = 5\%$  abnormal). Here we did not apply the 30 degree limbs elevation since the outcome is no



significant difference (13). PO device used was a pocket-size fingertip (ChoiceMMED Pulse Oximeter MD300C15D). This device measurement ranging from 70 to 99% with an accuracy at 80% to 99% +/-2%, approved by Food and Drug Administration(USA), PMDA (Japan) and CMDCAS (Canada).

Ankle brachial systolic index taken as ratio between ankle and brachial systolic pressure. At least 2 readings and lowest reading was taken (18). Blood pressure measurement (using POLYGREEN BLOOD PRESSURE MONITOR (KP7550), Germany) applied with suitable cuff to each limb at the arm and just above ankle region. ABSI is the ratio of systolic of the arm and ankle. Examination was repeated 3 times if there was no reading. According to ACCF/AHA guidelines (19), ABSI of less than 0.9 is considered having significant lower limb PAD of more than 50% stenosis. In this study we used  $\leq 0.9$  as abnormal, and  $>0.9$  as normal.

#### **3.4.4 Gold standard study**

CTA LL is the gold standard of assessing lower limb stenosis. Eligible patients recruited for second meeting in 2 to 4 week time to perform CTA LL. This cross sectional study of angiogram performed using Siemens Somatom Definition AS+ 128-slice (Erlangen, Germany, 2007) CT scanner at Radiology Department, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan. All the eligible subjects underwent the same imaging protocol consisting of scout, unenhanced, arterial enhanced and delayed image. Bolus tracking triggered at before abdominal aorta confluence, image obtained at delayed 8 seconds after contrast administration, 12 seconds angiogram run off than 11 sec foot to knee scan. Bolus was triggered at HU of 150. Parameters are kVp 120, Care Dose 4D reference mAs, craniocaudal (caudocranial in delayed images) with pitch value 1.2 and average acquisition time of 20. Contrast media used was low osmolar, non-ionic, 300mgI/ml (Omnipaque™) 100 to 120ml administered via preset CT scan injector through large bore intravenous brannula with 3 to