PREVALENCE AND ASSOCIATED FACTORS OF MICROALBUMINURIA IN THAI TYPE 2 DIABETIC PATIENTS.

SIRIMA MONGKOLSOMLIT

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Thesis
Entitled

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Sirima Mongkolsomlit

Miss Sirima Mongkolsomlit
Candidate

Sutthi Jaroenpitak

Dr. Sutthi Jaroenpitak,
Ph.D.(Dental Public Health)
Major-Advisor

Phitaya Ch, MD.

Assoc. Prof. Phitaya Charupoonphol,
D.V.M., M.D.,
D.T.M.& H., M.P.H.M.
Co-Advisor

Chukiat Viwatwongkasem.

Assoc.Prof.Dr. Chukiat Viwatwongkasem,
Ph.D.(Biostatistics)
Co-Advisor

P- Rawdaree

Dr. Petch Rawdaree, M.D.,
M.Sc.(Epidemiology)
Co-Advisor

Prof. M.R. Jisnuson Svasti, Ph.D.
Dean
Faculty of Graduate Studies

Kulaya Narksawat

Assoc.Prof. Kulaya Narksawat,
D.D.S.,M.P.H., M.S.(Med Epidemiology).
Chair
Master of Science (Public Health)
Major in Infectious Disease and
Epidemiology
Faculty of Public Health

Thesis
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For the degree of Master of Science (Public Health)
Major in Infections Disease and Epidemiology
on
3 October, 2006

Sirima Mongkolsomlit

Miss Sirima Mongkolsomlit
Candidate

Phitaya Ch, M.D.

Assoc.Prof. Phitaya Charupoonphol,
D.V.M., M.D.,
D.T.M.&H., M.P.H.M.
Member

Wisit Chaveepojkamjorn

Assoc.Prof. Wisit Chaveepojkamjorn,
D.V.M., M.P.H.
Chair

Chukiat Viwatwongkasem

Assoc.Prof.Dr. Chukiat Viwatwongkasem,
Ph.D.(Biostatistics)
Member

Sutthi Jaroenpitak

Dr. Sutthi Jaroenpitak,
Ph.D.(Dental Public Health)
Member

P. Rawdaree

Dr. Petch Rawdaree,M.D.,
M.Sc.(Epidemiology)
Member

Swangjit Suraamornkul

Dr. Swangjit Suraamornkul,M.D.,
M.Sc.(Clinical Investigation)
Member

Jisnuson Svasti

Prof. M.R. Jisnuson Svasti, Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

Phitaya Ch, M.D.

Assoc. Prof. Phitaya Charupoonphol,
D.V.M., M.D.,
D.T.M.& H., M.P.H.M.
Dean
Faculty of Public Health
Mahidol University

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Sirima Mongkolsomlit

PREVALENCE AND ASSOCIATED FACTORS OF MICROALBUMINURIA IN THAI TYPE 2 DIABETIC PATIENTS.

SIRIMA MONGKOLSOMLIT 4436097 PHPH / M

M.Sc.(PUBLIC HEALTH) MAJOR IN INFECTIOUS DISEASE AND EPIDEMIOLOGY

THESIS ADVISORS: SUTTHI JAROENPITAK, Ph.D.(DENTAL PUBLIC HEALTH), CHUKIAT VIWATWONGKASEM, Ph.D.(STATISTICS), PHITAYA CHARUPOONPHOL, M.D., D.V.M., D.T.M&H., M.P.H.M., PETCH RAWDAREE, M.D., M.SC.(EPID.)

ABSTRACT

Microalbuminuria represents the earliest clinical evidence of diabetic nephropathy and cardiovascular diseases, and is a marker of increased diabetic complications. There is evidence of decreasing prevalence diabetes complication. This analysis of Thai data from the Diabetes Registry Project(DRP) assessed the prevalence of microalbuminuria and identified risk factors associated with microalbuminuria in type 2 diabetes.

This was a cross sectional clinic-based epidemiological study and meta analysis. A total 8,913 registry type 2 diabetic patients in DRP were enrolled, of which 1,734 patients constituted the study group(patients under 18 years and who had not completed microalbuminuria tests were excluded). Studies of the prevalence of microalbuminuria reported between January 1980 and June 2006 by computer based searchs(Pubmed) were also conducted. This study identified 17 articles on microalbuminuria prevalence from the 80 included in the systematic review. The pooled prevalence of microalbuminuria for meta analysis showed 35.9%(95%CI 27.9-43.9). In this study, The prevalence of microalbuminuria was 53.4%(926). The mean age was 61.0$\pm$10.9 years, with mean duration of diabetes of 10.9$\pm$8.5 years. Sequential logistic regression analysis indicated that after adjustment for age and sex, only five variables were significantly associated with microalbuminuria: Systolic blood pressure $\geq$ 130 mmHg(OR=1.51; 95%CI, 1.13-2.16, P-value=0.007), HDL-C <40(male), <50(female)(OR=2.52, 95%CI, 1.52-4.21 P-value<0.001),duration of diabetes 5-9.9, 10.-14.9, 15-19.9 and $\geq$ 20 years(OR = 1.59, 95%CI, 1.08-2.34, P-value = 0.020, OR=2.38, 95%CI, 1.56-3.64, P-value < 0.001, OR=3.21, 95%CI, 1.95-5.31, P-value < 0.001, OR=2.17, 95%CI, 1.32-3.57, P-value =0.002), Smoking(OR=1.42, 95%CI, 1.03-1.96, P-value=0.034) and body mass index 25-29.9 and $\geq$ 30 kg/m^2(OR=1.57, 95%CI, 1.09-2.27, P-value=0.014, OR=2.09, 95%CI, 1.28-3.42, P-value=0.003). Awareness of microalbuminuria can assist the clinician in identifying diabetic patients at high risk of both micro-and macrovascular complications. Annual screening for microalbuminuria is recommended for all patients with type 2 diabetes.

KEY WORDS: MICROALBUMINURIA/ PREVALENCE/ TYPE 2 DIABETES / MULTICENTER / UMA/ COMPLICATION
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ความชุกและปัจจัยที่มีความสัมพันธ์กับไมโครแอลบูมินูเรียในผู้ป่วยเบาหวานชนิดที่ 2 คนไทย
(PREVALENCE AND ASSOCIATED FACTORS OF MICROALBUMINURIA IN THAI TYPE 2 DIABETIC PATIENTS.)

สิริมา มงคลสัมฤทธิ์ 4436097 PHPH / M

วท.ม. (สาธารณสุขศาสตร์) สาขาวิชาเอกโรคติดเชื้อและวิทยาการระบาด

คณะกรรมการควบคุมวิทยานิพนธ์: สุทธิ เจริญพิทักษ์, ท.บ., D.D.S., M.P.H., Ph.D.(ทันตสาธารณสุข), ชูเกียรติ วิวัฒน์วงศ์เกษม, Ph.D.(สถิติ), พิทยา จารุพูนผล, สพ.บ., M.D., D.T.M.&H., M.P.H., อ.ว.(เวชปฏิบัติทั่วไป), เพชร รอดอารีย์, พ.บ., วว.(อายุรศาสตร์ทั่วไป), อ.ว.(อายุรศาสตร์ต่อมไร้ท่อ), M.Sc.(ระบาดวิทยา), DLSHTM.

บทคัดย่อ

ไมโครแอลบูมินนูเรีย เป็นหลักฐานทางคลินิกที่บ่งชี้ว่าไตเริ่มมีความผิดปกติจากโรคเบาหวาน โรคหัวใจและหลอดเลือด และยังเป็นตัวบ่งบอกถึงการเพิ่มขึ้นของโรคแทรกซ้อนในผู้ป่วยเบาหวาน วัตถุประสงค์การวิจัยเพื่อศึกษาความชุกของไมโครแอลบูมินนูเรียในผู้ป่วยเบาหวานชนิดที่ 2 และศึกษาปัจจัยที่มีความสัมพันธ์กับไมโครแอลบูมินนูเรียในผู้ป่วยเบาหวานชนิดที่ 2 คนไทย ใช้วิธีการศึกษาแบบวิเคราะห์เมตาและการศึกษาแบบตัดขวาง โดยใช้ฐานข้อมูลโครงการลงทะเบียนผู้ป่วยเบาหวาน เป็นผู้ป่วยเบาหวานชนิดที่ 2 จำนวน 1,734 รายที่ได้รับการวิเคราะห์ตามเกณฑ์วิธีและทำการสืบค้นรายงานความชุกของไมโครแอลบูมินนูเรียในผู้ป่วยเบาหวานชนิดที่ 2 ที่ตีพิมพ์ในระหว่างเดือนมกราคม 2523 ถึง มิถุนายน 2549. ผลการศึกษาจากการสืบค้นข้อมูลด้วยวิธีการทบทวนวรรณกรรมอย่างเป็นระบบ 80 เรื่องมีรายงานการศึกษา 17 เรื่องที่นำมาใช้ในการวิเคราะห์เมตา พบความชุกของไมโครแอลบูมินนูเรียในผู้ป่วยเบาหวานชนิดที่ 2 ร้อยละ 35.9 ในคนไทยพบความชุกของไมโครแอลบูมินนูเรียร้อยละ53.4 อายุเฉลี่ย 61.0±10.9 ปี, ระยะเวลาป่วยเป็นเบาหวานเฉลี่ย 10.9±8.5 ปี ภายหลังวิเคราะห์โดยใช้ Sequential logistic regressionโดยควบคุมเพศและอายุ พบว่าปัจจัยที่มีความสัมพันธ์กับไมโครแอลบูมินนูเรียได้แก่ ความดันโลหิตค่าบน, ไขมันในเลือดชนิด HDL-C, ระยะเวลาป่วยเป็นเบาหวาน, การสูบบุหรี่ และดัชนีมวลกาย

การตรวจไมโครแอลบูมินนูเรีย สามารถช่วยให้ประเมินความเสี่ยงในการเกิดโรคแทรกซ้อนของหลอดเลือดในผู้ป่วยเบาหวานได้ จึงควรตรวจหาไมโครแอลบูมินนูเรียในผู้ป่วยเบาหวานชนิดที่ 2 ทุกปี

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CHAPTER I

INTRODUCTION

Rationale of the Study

Diabetes is a common chronic disease worldwide. In 1994, the International Diabetes Federation Directory(IDF)(1) estimated that over 100 million people worldwide had diabetes. Also in 1994, McCarty et al.(2) using data from population-based epidemiological studies, estimated that the global burden of diabetes was 110 million in 1994 and that it would double to 239 million by 2010. The World Health Organization(WHO)(3) also estimated the global burden of 135 million in 1995, which the number reaching 299 million by the year 2025. According to IDF estimates(4), which have been allocated into seven IDF regions: Africa(AFR), Eastern Mediterranean and Middle East(EMME), Europe(EUR), North America(NA), South and Central America(SACA), South-East Asia(SEA) and Western Pacific(WP), it affects approximately 194 million people worldwide in 2003. This is more than the 1995 WHO global estimation of 135 million, and 333 compared with 366 million people in 2025 by the IDF estimation(Table 1) and in 2030(5) respectively.

In Thailand, The IDF estimated prevalence of diabetes increased from 2% to 5% in 2000 to 2025(4). The World Health Organization estimated the number of Thai people with diabetes as 1,536,000 in 2000 and increase to 2,739,000 in 2030(5).

The IDF reconfirms the fact that type 2 diabetes constitutes about 85% to 95% of all diabetes cases in developed countries and accounts for an even higher percentage in developing countries. The vast majority of these people have type 2 diabetes. Type 2 diabetes is a major cause of premature morbidity and mortality, particularly from cardiovascular disease, blindness, amputations and renal failure. Its

long term complications both microvascular and macrovascular diseases lead to increased medical expenses, hospitalization and death in diabetic patients.

Table 1 The Prevalence of diabetes and impaired glucose tolerance (IGT).

All diabetes and IGT	2003	2025
Total world population(billions)	6.3	8.0
Adult population(billions)(age 20 –79 years)	3.8	5.3
Number of people with diabetes(millions)	194	333
World diabetes prevalence(%)	5.1	6.3

source: http://www.eatlas.idf.org/Prevalence/

Macrovascular complications in type 2 diabetes such as cardiovascular disease, cerebrovascular disease in people with type 2 diabetes shortened a life expectancy as much as 15 years, which up to 75% dying of macrovascular complications(6). For Microvascular complications, such as retinopathy, nephropathy and neuropathy, diabetic retinopathy is the leading causes of blindness, nephropathy is leading cause of renal failure and neuropathy is leading cause of amputation. The data from several studies reported prevalence of type 2 diabetic complications summarized in Table 2. Both Micro- and Macrovascular complications were the long term complications. There are many studies defined risk factors of diabetic complications and tried to develop guideline for screening risk factors in diabetic patients. At first, Many studies have confirmed that microalbuminuria is an early predictor of the renal insufficiency, then microalbuminuria is a marker for screening of diabetes nephropathy. Type 2 diabetes from the time of diagnosis should be screened annually for microalbuminuria. Later, there are several studies found that microalbuminuria was strongly associated with traditional cardiovascular risk factors and is a harbinger of later cardiovascular complications(26,10,11). Therefore, microalbuminuria is an important marker for more pronounced diabetic vascular diseases(7,8) and recently, Masoud et al.(9)

reported that prevalence of microalbuminuria in type 2 diabetic retinopathy was 5.9% and microalbuminuria was associated with diabetic retinopathy and a reliable marker of retinopathy.

A cross sectional study(9-17)in type 2 diabetes mellitus patients demonstrated a prevalence of microalbuminuria of 13.4-85.3%. Microalbuminuria in type 2 diabetes patients can be reduced and in long term studies suggested improvement of prognosis, especially with ACE-I as in the steno II study(18). It is important to examine the extent to which persons with diabetes should receive this screening. Detection of microalbuminuria can assist the clinician in identifying diabetic patients at risk for both micro- and macrovascular complications.

Table 2 The Prevalence of type 2 diabetic complications.

Complication	**Other Study**(%) (reference)	**DRP 2003(%)** (19)
Neuropathy	7.6 - 68.0 (20-27)	3.9(peripheral neuropathy)
Nephropathy	18.9 – 57 (16, 28-31)	43.9
Cardiovascular disease	5.1- 30.8 (20,23,32-34)	8.1
Cerebrovascular disease	4.1 - 6.7 (20.23,33)	4.4
Amputation	0.7- 4.8 (23,35-36)	1.6
Retinopathy	17.4 - 35.3 (21-22,25,36)	30.7

In Thailand, There are rare report about prevalence and associated factor of microalbuminuria in Thai type 2 diabetic patients. Therefore, I was to study these issues by using diabetic registry database in the Diabetes Registry Project.

Diabetes Registry Project(DRP) has been funded since 2003 by the Health System Research Institute(HSRI), Clinical Research Collaboration Network(CRCN) and the Endocrine society of Thailand. A registration of 9,419 diabetic patients expected to follow-up at 11 diabetic clinics in tertiary diabetic clinics in Bangkok and major provinces. The data of type 2 diabetes are collected from 8,913 participants. So the database of diabetes registry project is used in this study.

The purpose of this study were to identify associated factors of microalbuminuria in type 2 diabetes. This knowledge will be used to provide surveillance system and to develop appropriate strategy for prevention and control of the complications.

Objective

General objectives

To study prevalence, associated factors of microalbuminuria, in type 2 diabetes.

Specific objectives

1. To study prevalence of microalbuminuria in type 2 diabetes.

2. To identify risk factors associated with microalbuminuria in type 2 diabetes.

Scope of the study

This study defines association factor of microalbuminuria in Type 2 diabetes patients registration in multi-center registry of diabetic patients in 11 tertiary care hospitals and medical schools between April to December 2003, in a cross-sectional basis.

Assumption of the study

1. All of type 2 diabetic patients attended at diabetic clinic had been diagnosed by same standard method.

2. Diabetic Complication had been diagnosed by specialist of each site.

3. Blood pressure was measured twice, at least 1 minute apart, by automated blood pressure machine(Omron T4)

4. Laboratory results reported in the registry were collected from routine examinations of the institutes'clinical care which had been tested with past 6 months or in the following 3 months after registration.

Limitation of the study

This study is a sub-analysis of diabetes registry project, therefore this study will represent diabetic patient in tertiary hospitals.

Variables

Independent variables

HbA1c

Systolic blood pressure

Diastolic blood pressure

Body mass index

Lipid profile

Total cholesterol

high-density lipoprotein (HDL)

Low-density lipoprotein (LDL)

Triglycerides

Smoking

duration of diabetes

Control variables

The control variables, aged and sex, based on previously publications, were included in the logistic regression model.

Dependent variable

microalbuminuria

Definitions

Microalbuminuria(37) is a leakage of small amounts of protein (albumin) into the urine between 20 to 200 μg/minute or 30 to 300 mg/24 hours.

Type 2 diabetetes(38) is a heterogeneous group characterized by disorders of insulin resistance and insulin secretion. Patients were diagnosed when plasma glucose of 126 mg/dl or higher after an overnight fasting on more than one occasion or after 75 gram oral glucose, diagnostic values are 200 mg/dl.

Fasting Plasma Glucose(39) Also known as fasting blood sugar, the measurement of plasma glucose generally taken after an overnight fast. Level of fasting plasma glucose are classified according to the ADA guideline(40) as follows:

Acceptable 110 – 130 mg/dl, Uncontrol $\geq$ 130 mg/dl

Hba1c is a measure of how well patients are controlling their diabetes. Blood glucose binds to hemoglobin through a process called glycosylation. The higher the blood sugar the more glucose binds to the hemoglobin. A blood test can measure the amount of glycosylation that has occurred revealing the average blood glucose levels for the previous three to four months before the test. Level of glycemic control are classified according to the ADA guideline as follows:

Acceptable < 7 % , Uncontrol ≥ 7 %

Diastolic blood pressure - the lowest blood pressure measure in the arteries, which occurs between heartbeats. Level of diastolic blood pressure control are classified according to the ADA guideline as follows:

Acceptable < 130 mmHg , Uncontrol ≥ 130 mmHg.

Systolic blood pressure The highest arterial pressure measured during the heart beat cycle. It occurs when the heart muscle is contracting (pumping). Level of systolic blood pressure control are classified according to the ADA guideline as follows:

Acceptable < 80 mmHg , Uncontrol ≥ 80 mmHg.

Body mass index(BMI: Kg/m^2) is a unit of measurement to describe weight in relation to height for people 20 to 65 years of age. It indicates whether a person's size is in the low, moderate or high zone for developing health problems. WHO Asia-Pacific Region, definition(41) was measured by dividing the weight in kilograms by the square of height in meters and list of BMI are as the following:

Underweight	< 18.5	Kg/m^2
Normal range	18.5 – 22.9	Kg/m^2
At risk	23 – 24.9	Kg/m^2

Obese1	25 –29.9	Kg/m^2
Obese2	$\geq$ 30	Kg/m^2

Total Cholesterol is a type of fat which occurs naturally in our bodies and is also found in animal fats. Too much saturated fat and dietary cholesterol can cause the blood cholesterol to rise and collect along the inside walls of blood vessels as fatty build-up. Level of Total cholesterol control are classified according to the ADA guideline as follows:

High blood cholesterol defined as $\geq$ 200 mg/dl.

high-density lipoprotein (HDL): a composition of protein and lipid which is high in density(the "good" cholesterol) that promotes breakdown and removal of cholesterol from the body. Level of high-density lipoprotein control are classified according to the ADA guideline as follows:

Low level of high density lipoprotein are < 40 mg/dl in men and < 50 mg/dl in woman.

Low-density lipoprotein(LDL): a type of lipoprotein in the body; also known as "bad" cholesterol. LDL is considered a risk factor for heart disease. Level of low-density lipoprotein control are classified according to the ADA guideline as follows:

High level of low density lipoprotein defined as > 100 mg/dl.

Triglycerides High levels of triglycerides is > 150 mg/dl. Level of triglycerides control are classified according to the ADA guideline

duration of diabetes is defined as the duration from the diagnosis of diabetic to the time of entry the study. If the patients did not know the durations, It was checked from the medical record.

Smoking was classified as having never smoker if patients had not smoked in his/her lifetime, as being an Ex-smoker if he/she had smoked in lifetime but had stopped smoking before registry more than or equal to 1 year and as smoking if patients had smoked in his/her lifetime and not stopped.

CHAPTER II

LITERATURE REVIEW

Scope reviewing of literature is divided into 3 parts as follows.

1. Diabetes mellitus

2. Microalbuminuria

3. The research relevant to diabetes complications, Pharmacological Treatment and microalbuminuria

Diabetes mellitus

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves.

Classification of Diabetes

Diabetes is classified into one of the following four general categories.

1. Type 1 diabetes is a disease resulting from absolute insulin deficiency usually caused by autoimmune destruction of pancreatic islet cells. Type 1 diabetes can occur at any age. The initial clinical presentation may be ketoacidosis with an acute illness or a more gradual presentation with symptoms of hyperglycemia. Other autoimmune disorders may also be present such as Addison’s disease, thyroiditis, and pernicious anemia.

2. Type 2 diabetes is a disease of uncertain etiology resulting from a relative, but not absolute, insulin deficiency with an underlying insulin resistance. Type 2 diabetes increases with obesity, age, and physical inactivity.

3. Uncertain can not define

4. Other include genetic defects of islet cell function, genetic defects in insulin action, endocrinopathies such as Cushing's disease or syndrome, drug or chemical induced hyperglycemia, infections and Gastational diabetes.

Diagnosis of diabetes

1. Fasting Plasma Glucose. This is the preferred test for diabetes. To have this test, you have to fast at least eight hours or overnight. You will have a blood sample drawn and examined for glucose. Most people have a level between 70 and 110 milligrams of glucose per decilitre of blood. A level of 126 mg/dl or higher on two tests given on two different days confirms a diagnosis of diabetes. (Previously a level of 140 mg/dl or higher was used to diagnose diabetes, but in 1997, the guidelines were revised because by the time a person got a diagnoses of diabetes with a level of 140 mg/dl, serious damage to the body had often already occurred. By lowering the diagnostic levels to 126 mg/dl, early control of the disease can begin and risk of complications is lower.)

2. Oral Glucose Tolerance Test. For this test you have to fast at least eight hours and not have smoked or drank coffee. Your fasting plasma glucose is tested from a blood sample. After the test you will be asked to drink a sweet glucose syrup and then your glucose level will be measured from a blood sample taken two hours after you drink the liquid. There can be up to four blood samples taken to measure the blood glucose level. The American Diabetes Association expert committee recommends that this test be eliminated because it is a difficult and time-consuming test.

Sign and Symptoms

Type 1 DM. Frequent urination (in children, a recurrence of bed-wetting after toilet training has been completed). Unusual thirst, especially for sweet, cold drinks. Extreme hunger. Sudden, sometimes dramatic, weight loss. Weakness. Extreme fatigue. Blurred vision or other changes in eyesight. Irritability. Nausea and vomiting (acute symptoms).

Type 2 DM. increased production of urine (the body is trying to get rid of the excess glucose in the urine) unusual thirst , tiredness (because the glucose is "going to waste" and not being converted into energy),loss of weight , increased appetite ,feeling sick , blurred vision , infections such as thrush or irritation of the genitals

Microalbuminuria

Microalbuminuria is still the only early abnormality of the diabetic kidney that has an established prognostic value. Microalbuminuria evolves into clinical nephropathy and renal failure in a majority of cases of insulin-dependent diabetic patients, and is defined by the detection of urinary albumin excretion rates of 20–200 μg/min in timed urine collections. The occurrence of microalbuminuria at rates of 5–27 % of non-proteinuric patients and cost-benefit considerations justify the screening for microalbuminuria in diabetic outpatient clinics. Both near-normalisation of glycaemic control and treatment with ACE-inhibitors are indicated in patients with insulin-dependent diabetes to correct the progression of micro- to macroalbuminuria. Other therapeutic perspectives are being considered, but the current notion that the available therapies may not arrest the course of nephropathy at this stage suggests that earlier interventions may be required. Prevention of microalbuminuria and overt nephropathy may require a primary approach to the subset of patients with a genetic predisposition to this complication, and several studies (candidate gene or genomic scan with microsatellite probes) now address the chromosomal loci and the nature of the genes that may involved.

Urinary albumin levels can vary widely from sample to sample in the same patient, with day-to-day intraindividual coefficients of variation as high as 50%. Factors that can increase urinary albumin excretion include urinary tract infection, congestive heart failure, exercise, fever, poor glycemic control, and vaginal discharge(42) By obtaining a first morning sample we can minimize at least the effect of exercise.

The American Diabetes Association and The Endocrine society of Thailand demand at least two elevated albumin to creatinine ratio by 3 or 6 months to make the diagnosis of microalbuminuria(43). There are several laboratory methods for measuring urinary albumin excretion. All of them appear to have similar sensitivity and specificity(44).

Prevalence of Microalbuminuria in type 2 diabetes

The Prevalence for microalbuminuria in type 2 diabetes patients have been determined in many population(Figure 1). It have been described in different studies. The report prevalence of microalbuminuria was quite similar, ranging from 13.4 % to 85.3%(Table 3). The proportion of patients with type 2 diabetes who develops microalbuminuria is substantial namely 25% after 10 years(13).

Table 3 Prevalence of microalbuminuria in type 2 diabetes in several study design.

Author(Ref)	Definition	population	study design	Prevalence (%)
Dasmahapatra et al.(45)	Time collection (20-200 μg/min)	African-American	Cross-sectional (n=116)	31
Klein et al. (46)	UAC (30-300 mg/L)	American	population age > 30 years(n=798)	26

Table 3 Prevalence of microalbuminuria in type 2 diabetes in several study design. (Continued)

Author(Ref)	Definition	population	study design	Prevalence (%)
Ahmedani (47)	Micral test strip II	Pakistan	Cross-sectional study (n= 2,100)	34.0
Hashim R.(48)	UAC (30-300 mg/L)	Lahore	Cross-sectional study (n= 150)	46.7
Leza-Torres (49)	UAC (30-300 mg/L)	Coahuila	Cross-sectional study (n= 301)	85.3
Peera(50)	Micral test	Thai	Cross-sectional study (n= 97)	43.3
Mattock et al. (53)	Time collection (20-200 μg/min)	English	cross-sectional cohort follow-up(n=141)	25
Alzaid et al.(30)	24 hour (30-300 mg/24 hour)	Saudi Arabian	Cross-sectional (n=184)	41.3
Onyechi(11)	UAC (30-300 mg/L)	Bahraini	Cross-sectional study (n=312)	25
Varghese A. (12)	UAC (30-300 mg/L)	South India	Cross-sectional study (n=1,425)	36.3
TKW(13)	Clinitek 50 testing	Hong Kong	Cross-sectional study (n= 1,161)	13.4
Lee KU(14)	Time collection (20-200 μg/min)	Koreans	Cross-sectional study (n= 631)	20.0
Bruno G.(15)	Time collection (20-200 μg/min)	Italy	Cross-sectional study (n= 1,967)	32.1
Erasmus RT (16)	24 hour (30-300 mg/24 hour)	Nigreria	Cross-sectional study (n= 113)	56.5
Annemilke(17)	UAC (30-300 mg/L)	Amsterdam	Cross-sectional study (n= 195)	17.2
Masoud R.M (9)	Clinitek 100 testing UAC (30-300 mg/L)	USA	Cross-sectional study (n= 590)	25.9

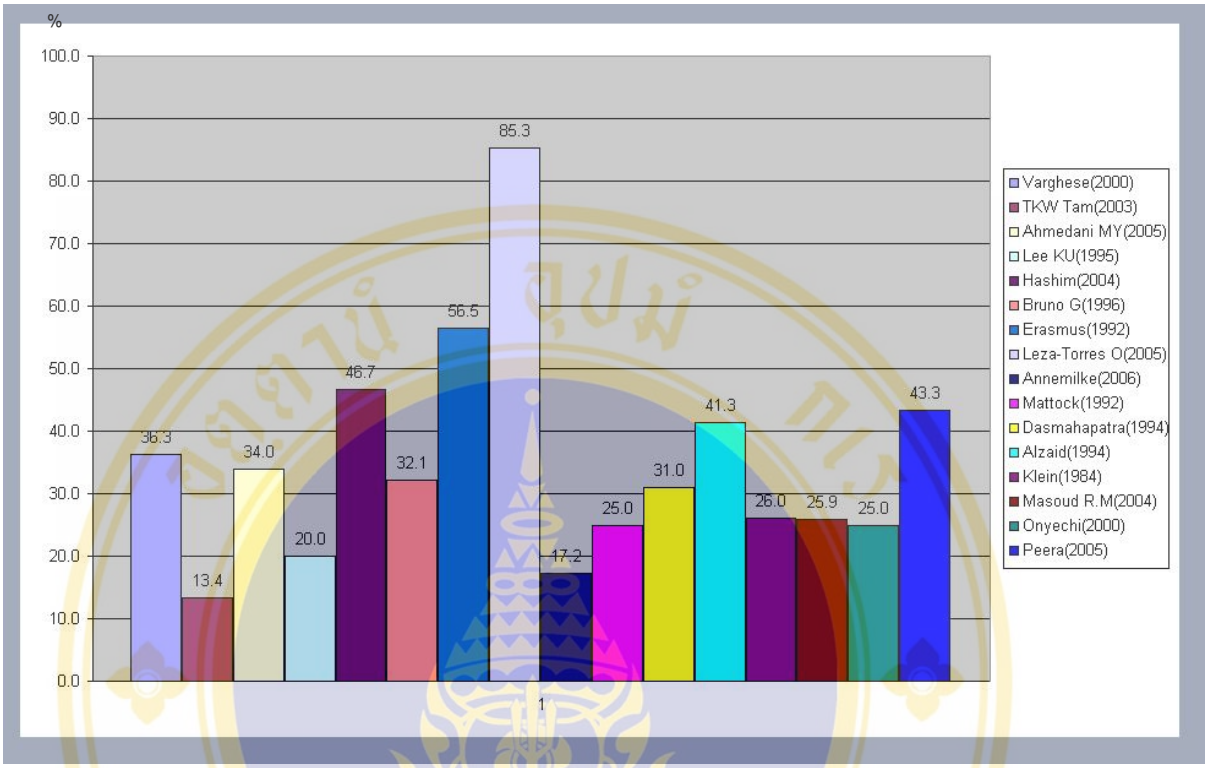

Figure 1. Prevalence of microalbuminuria in type 2 diabetes

Screening for microalbuminuria can be performed by three methods: 1. measurement of the albumin-to-creatinine ratio in a random spot collection; 2. 24 hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and 3. timed collection.

The ADA has recommened cutoffs for each of the three tests to determine microalbuminuria. Table 4 displays the unit for reporting these tests. Random or spot tests for microalbumin concentration are not recommened. Because of the inherent variation in urine albumin excretion, most authorities also recommend that irine albumin levels be measured in 2 out of 3 collections within a 3 to 6 month period before a patient with diabetes is diagnosed as having microalbuminuria. The ADA's suggested clinical algorithm for microalbuminuria screening is displayed in figure 2.

Table 4 The American Diabetes Association(ADA) recommened tests for microalbuminuria and the recommended units and cutoffs.

	24 hour collection (mg/24 hours)	Timed collection (μg/minute)	Random A/C ratio (μg/mg Cr.)
Normal	< 30	< 20	<30
Microalbuminuria	30-300	20-200	30-300

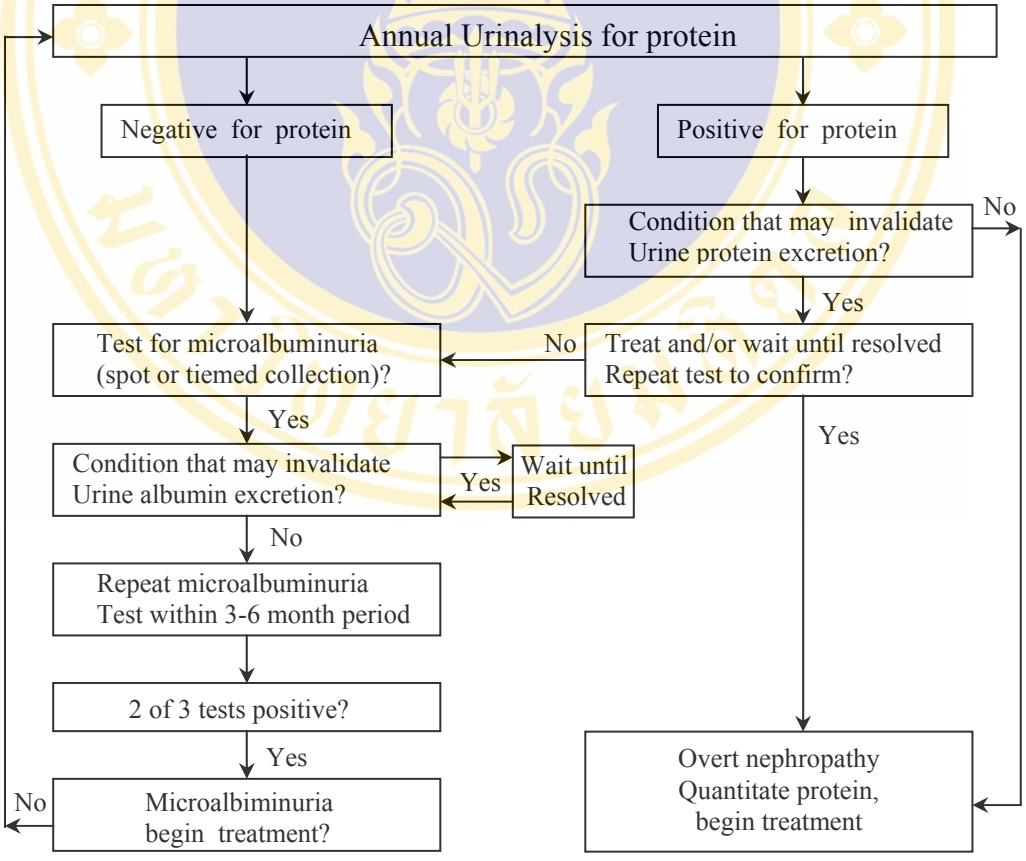

Figure 2. The American diabetes Association's suggested clinical algorithm for microalbuminuria screening.

Measurement

Both quantitative and qualitative methods of measuring microalbuminuria are now available. Quantitative ways of determining urinary concentrations of very small amounts of albumin usually involve radioimmunoassay which have high sensitivity and specificity. Qualitative tests, which are adequate for screening for microalbuminuria, are readily available for use in the physician's office. They include latex bead immunoagglutination and test tablets such as the Micro-bumin test.

Mortality/morbidity of Microalbuminuria

Dinneen and Gerstein(51) carried out a systematic review of the literature (with meta-analyses) analyzing the association between microalbuminuria, total mortality, cardiovascular mortality and cardiovascular morbidity in individuals with Type 2 diabetes. Original articles were assessed for inclusion in the review on the following predefined criteria: Type 2 diabetes was clearly defined; microalbuminuria was not assessed in the presence of bacteriuria; main outcomes (death, myocardial infarction and stroke) were clearly defined; other risk factors for atherosclerotic disease were assessed; completeness of follow up was reported. The outcomes from 11 included cohort studies were summarized as odds ratios and these data were pooled to give an overall outcome for the studies. Data were reported for a total of 2,138 patients who were followed up for a mean of 6.4 years. Patient age was similar across cohorts (age range: 52-75 years). All studies were carried out in Europe. There was heterogeneity between the primary studies with respect to the methods for measuring albumin. Four studies collected early morning urine samples, one used a daytime sample, three studies collected timed overnight urine samples, one study collected a timed 24-hour urine specimen and two other studies collected shorter timed specimens. This led to a variation in definitions of microalbuminuria between studies. Even where the same urine collection method was followed there was not always consistent levels of albumin used to define microalbuminuria. Microalbuminuria was defined as an albumin excretion rate(AER) of 35 – 389 mg/24h in a 24 hour urine sample(52). In

studies using overnight urine samples as the method for detecting albumin excretion, 20 – 200 μg/min was the range

In Mattock et al.(53), while two studies quoted cut off points of >10.5 μg/min (54) and >31 μg/min (55). When shorter timed collections were used in two studies, a cut off point of >15 μg/min and 15 – 200 μg/min defined microalbuminuria (56, 57). The studies using spot urine samples to measure albumin concentration had different ranges to define microalbuminuria. These various methods of urine collection may have contributed to the range in prevalence for microalbuminuria of between 12% and 36% in the eight studies in which prevalence rates could be measured. Seven of the studies were based in a hospital setting and four were performed in a general practice setting or were population based. There were probably selection biases operating in most of the studies included in the review as only two attempted to recruit a sample truly representative of people with Type 2 diabetes in the community(58, 59). The populations in the individual studies were all made up of people with Type 2 diabetes. There was variation in mean duration of diabetes in the different cohorts, ranging from newly diagnosed to thirteen years. However, in seven of the studies the mean duration was between 5.5 years and 8.5 years. The length of follow up was different in the various studies included in the review, ranging from one year to 13 years, with a mean follow up time of 6.4 years. A follow up period of one year was sufficient for the events of interest(i.e. total mortality, cardiovascular morbidity and mortality) to occur. Clearly, there was heterogeneity between the included studies in terms of length of follow up, methods used for assessing microalbuminuria, and duration of diabetes in the study populations. However, there was a consistent message from the outcomes of the studies. In ten of the eleven studies reporting total mortality there was a positive association between microalbuminuria and death.

Progression in patients from microalbuminuria

In the study by Wirta et al.(60), twenty six patients of 108 who were followed up had microalbuminuria at baseline. Twelve of these still had microalbuminuria (46%) while five had developed proteinuria (19%) over the six years. Nine of the subjects with microalbuminuria at baseline had a normal albumin excretion rate (AER)

at follow up. Regression to normoalbuminuria was predicted by low blood pressure although only one of these nine subjects began drug therapy for high blood pressure during the study period.

In the study by Niskanen et al.(59), 26(16%) subjects had microalbuminuria from the cohort of 133 Finnish general practice patients with newly diagnosed Type 2 diabetes. Five years later, of 108 followed-up, 9(43%) of the 26 with baseline albuminuria had reverted to a normal albumin excretion rate and 12(57%) had persistent microalbuminuria. There were no significant differences between the nine who reverted and those with persistent microalbuminuria in terms of age, sex, body mass index and blood pressure. A similar reversion in microalbuminuria was seen by Patrick et al.(61). In this study 149 people newly diagnosed with Type 2 diabetes from a hospital in Scotland had their albumin:creatinine ratio measured in an early morning urine specimen on diagnosis of diabetes. Microalbuminuria was defined as an albumin:creatinine ratio (ACR) >2.5 mg/mmol, while normoalbuminuria was defined as an albumin:creatinine ratio 2.5 mg/mmol. In the next 12 months the patients had a further three early morning urine samples analysed. If two or more of these showed an ACR >2.5 mg/mmol then persistent microalbuminuria was diagnosed. If only one showed an ACR >2.5 mg/mmol then the patient was defined as having intermittent microalbuminuria. The remainder of patients were termed as normoalbuminuric. Fifteen patients were lost to follow up and five were excluded due to initiating insulin therapy in the year after diagnosis of diabetes. Of the 129 patients in the Patrick study with complete data available, 88(68%) were defined as having normoalbuminuria, 20(16%) as having intermittent microalbuminuria and 21(16%) as having persistent microalbuminuria. Within the group with persistent microalbuminuria 18(86%) had had an elevated albumin:creatinine ratio at baseline, the other three were initially normoalbuminuric. Among the rest of the patients with microalbuminuria at baseline (N=21), eight were lost to follow up, three had intermittent microalbuminuria and 10 had consistently normal albumin excretion. In the 10 patients who reverted to normal urine albumin excretion after follow up, there was a significant trend for higher glycosylated haemoglobin at baseline compared with the group with persistent microalbuminuria ($p<0.05$).

The Research Relevant to microalbuminuria in type 2 diabetes

Age

Ravid et al.(62) examined 574 people with Type 2 diabetes who were initially free of abnormal albumin (albumin concentration <0.3 mg/24h), for a mean period of 7.8 years. The study found that, after adjustment for other variables, older age was significantly associated with the degree of albuminuria(>300 mg/24h) in this population, drawn from a diabetes clinic in Israel ($p<0.001$).

Gall et al.(63) followed 176 people with Type 2 diabetes with normal albumin excretion rates (<30 mg/24h) for nearly six years. For an increase in age by one year a patient had a relative risk of developing microalbuminuria (AER = 30 - 299 mg/24h) or proteinuria (AER > 300 mg/24h) of 1.07 (95% CI: 1.02 - 1.12, $p<0.01$), after adjustment for other risk factors.

Sasaki et al.(64) evaluated 1196 patients from a medical centre in Japan for a mean follow-up period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Age at entry into the study was found to significantly predict the development of Albustix positive albuminuria ($p<0.01$), after adjustment for other risk factors.

Davies et al.(6) used the UKPDS data to see if age at diagnosis of Type 2 diabetes affected diabetic tissue damage during the first six years of diabetes. Urinary microalbuminuria and creatinine concentrations were measured after six years. Microalbuminuria was taken as a urine creatinine regression-corrected concentration of >50 mg/l. From 5102 newly diagnosed Type 2(NIDDM) patients, the patients included in the analysis were 3027 white patients aged between 35 and 65 years with data available over 6 years. Patients were divided by age at entry into five consecutive age groups (36 - 41, 42 - 47, 48 - 53, 54 - 59 and 60 - 65 years). Age at diagnosis was not a significant marker for development of microalbuminuria at the six year follow up ($p=0.09$) or for initial prevalence of microalbuminuria at baseline ($p=0.41$).

In Wirta et al.(60) age at baseline was investigated as a predictor of progression to microalbuminuria (albumin excretion rate >30 mg/24h) and proteinuria (albumin excretion rate >300 mg/24h). The relationship between age at baseline and progression to either microalbuminuria or proteinuria was not statistically significant.

Niskanen et al.(59) also found that age at baseline did not predict development of microalbuminuria (albumin excretion rate >30 mg – 300 mg/24h) in 133 people with newly diagnosed diabetes.

Schmitz et al.(65) followed 178 people with Type 2 diabetes for four years. The cohort was selected from an outpatient clinic in Denmark. Age was not found to correlate with progression of albuminuria after adjustment for other independent factors. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration 15 mg/l) to microalbuminuria (urinary albumin concentration >15 mg/l to 200 mg/l) and from microalbuminuria to proteinuria (>200 mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. Age was not a significant factor in the development of proteinuria after 10 years, in a cohort of people with Type 2 diabetes who were free of proteinuria at baseline(60). Similarly age was not a predictor of albuminuria progression in 349 patients followed up for 5 years, after adjusting for other confounders (66).

Summary, The evidence of an association between age and proteinuria is conflicting, although the largest study found no association at 6 year follow up.

Blood glucose

In Niskanen et al.(59) 133 people with newly diagnosed Type 2 diabetes were randomly selected from the population register of an area in Eastern Finland. The cohort was examined at recruitment (baseline exam) and then twice more, after five years and 10 years (n=88, 36 deaths, 9 missing data). The patients were assessed for microalbuminuria (defined as urine albumin excretion rate of 30 mg/day or 20 μg/min) at each examination. Haemoglobin A_{1c} (HbA_{1c}) levels were significantly predictive of microalbuminuria at 10 years (p=0.003), as was fasting plasma glucose (p=0.009), after adjustment for age, insulin and blood pressure.

Mattock et al.(53) found, after age adjustment, that fasting plasma glucose levels were significantly associated($p<0.05$) with the development of microalbuminuria in 29 of 100 Caucasian patients, who attended a diabetes clinic in

London in a single year, (adjusted odds ration 2.27, 95%CI 1.33–3.88). Microalbuminuria was defined as 20 – 200 μg/min albumin excretion rate in an overnight urine sample, on at least two occasions at either of the two follow up examinations (three and seven years after baseline).

Klein et al.(67) examined the 10 year incidence of proteinuria in a population based cohort in the United States. A total of 1,370 patients with older onset diabetes (674 on insulin, 696 not on insulin) were examined at entry into the study and then followed up on two further occasions (at four years n=987; at ten years n=533). In people with older onset diabetes treated with insulin at 10 year follow up, the incidence of gross proteinuria (albumin concentration measured by reagent strip 0.3 μg/l) was significantly higher (odds ratio = 1.20, 95% CI 1.02 - 1.42) in those with higher glycosylated haemoglobin level. In those with older onset diabetes not on insulin, a glycosylated haemoglobin level 8.7% (odds ratio 2.17, 95% CI 1.30 – 3.61) was significantly associated with higher incidence of gross proteinuria at 10 years. A second large prospective study of 574 patients followed up for a mean of 7.8 (standard deviation 0.9) years has been carried out in Israel(62). Multiple regression analysis identified HbA_{1c} as one of three determinants of the subsequent decline in renal function. The risk for microalbuminuria was also predicted by the initial values of HbA_{1c}, among others. In 46 patients with Type 2 diabetes who had been monitored every two months for a mean of 4.5 years (range 3 - 6) at a diabetes clinic in South Korea, HbA_{1c} was found to be a significant predictor (odds ratio = 2.03, 95% CI 1.17 - 4.16, p=0.023) for development of overt proteinuria, after adjustment for various factors.

Of two Japanese studies, one found that in Type 2 patients followed for six years, those patients developing microalbuminuria (albumin excretion rate 20 μg/min), had significantly higher blood glucose levels than those who remained normoalbuminuric($p<0.01$). The relative mean level of blood glucose over the six years was 8.1 mmol/l . SD 0.9 in the subset remaining normoalbuminuric and 9.0 mmol/l SD. 0.9 in the subset developing microalbuminuria. However, the second Japanese study, evaluating 1196 patients from a medical centre in Japan for a mean period of 10 years, found that fasting plasma glucose did not significantly (at the

$p<0.05$ level) predict the development of Albustix positive albuminuria, after adjustment for sex, age, duration of diabetes, systolic blood pressure, obesity, diabetic retinopathy and insulin. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline(54).

In the United Kingdom Prospective Diabetes Study(68) 3,867 people with newly diagnosed Type 2 diabetes were randomised to either conventional blood glucose control or intensive blood glucose control. After nine years of follow up, a significantly greater percentage of people in the conventional treatment group had progressed to microalbuminuria ($p=0.0006$) and to proteinuria ($p=0.03$), compared to the intensive group. Over 10 years, the HbA_{1c} levels were 7.0% in the intensive treatment group and 7.9% in the conventional group. Microalbuminuria in this study was defined as urinary albumin concentration 50 mg/l, due to storage of samples at –20 Cencies. Proteinuria was defined as an albumin concentration 300 mg/l.

Schmitz et al.(65) assessed the relationship between HbA_{1c} and the progression of albuminuria over four years, in 178 people with Type 2 diabetes. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration 15 mg/l) to microalbuminuria (>15 mg/l - 200 mg/l urinary albumin concentration) and from microalbuminuria to proteinuria (urinary albumin concentration >200 mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. Progressors had poorer glycaemic control (HbA_{1c} 8.2%. 1.5 vs 7.7. 1.3, $p<0.05$) compared with non progressors. However a multiple regression analysis in patients with at least four years and (complete) 6 years of follow-up found that HbA_{1c} was not a significant predictor of rate of increase in albuminuria.

In Beilin et al.(69), 666 patients with Type 2 diabetes were followed for several years, in a hospital diabetes clinic in Australia. Glycated haemoglobin was significantly associated with urine albumin levels >30 mg/l ($p= 0.0001$) after adjustments for other risk factors (adjusted odds ratio = 1.242). Finally, Gall et al.(63) followed 176 people with Type 2 diabetes and normal albumin excretion rates (AER <30 mg/24h) for 6 years. A 1% difference in mean HbA_{1c} meant a patient had a relative risk of developing microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria

(AER >300 mg/24h) of 1.2 (95%CI: 1.1 - 1.4). This was significant at the $p<0.05$ level.

Conversely, four studies did not identify blood glucose as a risk factor for renal disease(55). Wirta et al.(60) observed the mean blood glucose of 150 people with recently diagnosed Type 2 diabetes. The patients were drawn from a diabetes clinic in Finland and were followed for six years. The link between blood glucose and progression of urine albumin excretion rate (AER) was measured. Progression of AER was defined as the development of microalbuminuria (AER = 30 – 300 mg/24h) from normoalbuminuria at baseline, or development of proteinuria (AER >300 mg/24h) from microalbuminuria at baseline. Mean blood glucose was not found to significantly influence the progression of AER (at the $p<0.05$ level of significance). In a prospective follow-up study of 37 Type 2 patients, HbA_{1c} was not associated with a decrease in the rate of creatinine clearance after adjustment for 4 other independent factors. Blood glucose was not found to be a predictor of albuminuria progression, after adjustment for other factors in patients with Type 2 diabetes in India(55). The authors followed up a cohort of 481 Type 2 patients prospectively for 5 years. Progression of albuminuria was defined as development of microalbuminuria (>20 μg/min - 200 μg/min) and proteinuria (>200 μg/min) and a significant increase in albuminuria within the microalbuminuric range.

Summary, There is a close association between the level of HbA_{1c} and progression of microalbuminuria.

Gender

In Gubbio cohort, risk for microalbuminuria was grater for men than than for women. This could reflect an influence of sex hormones on glomerular function(70). In a study by Gall et al.(63), male sex conferred a relative risk for developing microalbuminuria (AER = 30 - 299 mg/24h) or proteinuria (AER > 300 mg/24h) of 2.6 (95% CI: 1.2 - 5.4) compared with women ($p=0.02$). Sasaki et al.(64) evaluated 1,196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline.

Male sex was found to significantly predict the development of Albustix positive albuminuria ($p<0.01$), after adjustment for other risk factors. Ravid et al.(62) surveyed 574 people with Type 2 diabetes, drawn from a diabetes clinic in Israel. After a mean follow up period of 7.8 years they did not find sex to be a significant factor in the development of microalbuminuria (AER 30 – 300 mg/day) or proteinuria (AER >300 mg/day), after adjustment for other variables.Sex was not a significant factor in the development of proteinuria after 10 years, in a cohort of people with Type 2 diabetes who were free of proteinuria at baseline(60). This finding was confirmed in 172 people with Type 2 diabetes followed for four years in Schmitz et al.(65). Sex did not correlate with progression of albuminuria in this cohort selected from an outpatient clinic in Denmark.

Summary, The evidence is equivocal that male sex has an increased association with increased albumin excretion.

Blood pressure

Schmitz et al.(65) measured systolic and diastolic blood pressure in 278 people with Type 2 diabetes, from a clinic in Denmark. The influence of these two variables on progression of renal disease was measured. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration 15 mg/l) to microalbuminuria (urinary albumin concentration (>15 mg/l to 200 mg/l) and from microalbuminuria to proteinuria (urinary albumin concentration >200 mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. Systolic blood pressure was a significant predictor of rate of increase in albuminuria in 178 patients followed up after four years ($p=0.012$), and 135 patients followed-up for 6 years ($p=0.009$), in both cases after adjustment for average UAE, sex, age, BMI, plasma glucose, HbA_{1c}, diastolic blood pressure and baseline albuminuria.

In Beilin et al.(69) 666 people with Type 2 diabetes were followed for seven years in a hospital diabetes clinic in Australia. A significant association of systolic blood pressure with urine albumin >30 mg/l ($p=0.001$) was found after adjustment for other risk factors, and no association for diastolic blood pressure. The UKPDS(68) found an association, after adjustment for age, between systolic blood pressure

($p<0.0001$) and urine albumin excretion in 585 patients followed from 3 months to 3 years.

In Nielsen et al.(71) 24 hour ambulatory blood pressure (systolic and diastolic) was measured at baseline (n=32) and then after a mean period of 4.6 years, (n=23) in people with Type 2 diabetes from a hospital clinic in Denmark. At the same time, urine albumin excretion rate was calculated from the mean of two 24 hour urine collections of the 23 patients followed up. Eleven patients had normoalbuminuria (albumin excretion rate <15 μg/min) and twelve patients had microalbuminuria (albumin excretion rate = 15 – 200 μg/min) at baseline. The nine patients lost to follow-up had similar baseline UAE values to those followed up. Annual progression in UAE was significantly determined by increases in systolic ($p<0.008$) and diastolic ($p<0.033$) 24 hour ambulatory blood pressure after adjustment for other independent variables. Furthermore, albuminuria increased significantly in patients taking no or a stable dose of antihypertensive therapy(n=9) compared with that in those who initiated or increased antihypertensive therapy during the follow-up (n=13) ($p=0.02$), [1.144 (95% CI 0.999 - 1.310) ratio/year versus 0.938 (95% CI 0.839 - 1.048) ratio/year].

In a study of 574 people with Type 2 diabetes of less than five years duration (mean duration 1.92 $\pm$1.2 years), initially normotensive and with normal UAE, mean blood pressure at baseline was found to be a significant ($p<0.05$) determinant for the development of microalbuminuria (albumin excretion rate 30 – 300 mg/24h) and for duration to development of icroalbuminuria after adjustment for other risk factors. The participants were drawn from a diabetes clinic in Israel and were followed for a mean of seven years (range 2 - 9 years) (52).

Tanaka et al.(72) studied 123 Japanese patients with Type 2 diabetes for six years. Patients were matched for age and duration of diabetes, and recruited from an outpatient clinic. At baseline 74 were normoalbuminuric (albumin excretion rate 20 μg/min) and 49 had microalbuminuria (albumin excretion rate 20 μg/min - <200 μg/min). The association of blood pressure with development of microalbuminuria and progression to proteinuria (albumin excretion rate>200 μg/min) was measured. Mean diastolic and systolic blood pressures were significantly higher in those who progressed from microalbuminuria to proteinuria both at baseline and at six year

follow-up. A geographically close study was reported from South Korea(73). The authors found that mean systolic blood pressure was a significant predictor (odds ratio = 1.95, 95% CI 1.09 - 3.97, p=0.038) for development of overt proteinuria (UAE>200 μg/min on two consecutive occasions).

Forty-six patients were monitored for a mean of 4.5 years (range 3 - 6). Klein et al.(46) assessed the influence of a baseline blood pressure measurement upon the incidence of proteinuria after 10 years, in people with older onset diabetes. The participants were assessed separately according to whether they were on insulin therapy or not. In the group who were not taking insulin, a baseline systolic blood pressure reading of 146 mmHg was significantly associated (odds ratio = 2.47, 95% CI 1.49 - 4.09; $p<0.05$) with the development of proteinuria (defined as albumin concentration 0.3 g/l measured by reagent strip). Baseline blood pressure was not significantly associated with the development of proteinuria in people with older onset diabetes who were on insulin therapy. Although seven studies found an association between blood pressure and renal disease, a further six, looking at the same issue, found no significant association between the two.

Sasaki et al.(64) evaluated 1,196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Systolic but not diastolic blood pressure was found to significantly predict the development of Albustix positive albuminuria ($p<0.01$).

Niskanen et al.(52) followed up 133 newly diagnosed people with Type 2 diabetes for 10 years. They failed to find a significant association at the level of significance($p<0.05$) between either systolic blood pressure or diastolic blood pressure, and the development of microalbuminuria (albumin excretion rate >30 – 300 mg/24h) or proteinuria (>300 mg/24h).

Wirta et al.(60) reported that mean baseline arterial blood pressure was not a significant predictor of progression of urine albumin excretion rate at follow-up in those patients with Type 2 diabetes who were normoalbuminuric at baseline or of proteinuria in those patients either normo or microalbuminuric at baseline (109 subjects were followed up for 6 years).

Gall et al.(63) also found that neither systolic or diastolic blood pressure significantly predicted the development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER >300 mg/24h). In this study 176 normoalbuminuric white patients with Type 2 diabetes, from a hospital in Denmark, were followed for a median of 5.8 years.

Mattock et al.(53) examined the predictive influence of diastolic and systolic blood pressure upon the development of microalbuminuria (defined as an albumin excretion rate 20 μg/min) in 100 people with Type 2 diabetes, who had normal albumin excretion rates at baseline. The patients were drawn from a diabetes clinic in London and were followed for a minimum of three years and a maximum of seven years. Neither systolic (odds ratio 1.33, CI 0.80 - 2.21) nor diastolic (odds ratio 1.25, CI 0.81 - 1.95) blood pressure were found to be a significant factor (at the $p<0.05$ level) in the development of microalbuminuria.

In a prospective first year study of 481 people with Type 2 diabetes, blood pressure was not found to be a predictor of albuminuria progression, after adjustment for other factors (66).

Overall, the better designed studies found that progression to microalbuminuria and proteinuria was associated with higher levels of systolic blood pressure. Fewer studies also found an association with higher levels of diastolic blood pressure. There are 2 or 3 large clinical trials showed that reduction of blood pressure associated with urine microalbuminuria.

Duration of diabetes

John et al.(66) examined 481 consecutive Type 2 patients attending a diabetes clinic in a hospital in South India. The effect of duration of diabetes upon progression of urine albumin excretion rate(AER) after five years was measured. Progression was defined as a movement from normoalbuminuria(AER 20 μg/min)to microalbuminuria (>20 – 200 μg/min) or from microalbuminuria to proteinuria (>200 μg/min). A factor three increase in AER within the microalbuminuric range was also classed as a progression within this range. Duration of diabetes was significantly associated with progression of albuminuria ($p<0.01$).

In a six year follow up study of 176 people in Denmark with Type 2 diabetes, Gall et al.(63) did not find duration of diabetes to be significantly predictive in the development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER > 300 mg/24h). Similarly, Sasaki et al.(64) found, in a study of 1,196 Japanese Type 2 patients, followed up for a mean of ten years, duration ofdiabetes to not be significant risk factor related to the development of persistent albuminuria, after adjustment for seven other risk factors. A third study of 46 patients in South Korea also found no relationship (odds ratio = 1.46, CI 0.85 - 2.72, p=0.181) between duration of diabetes and overt proteinuria, after adjustment for other variables (73).

The evidence of a link between duration of diabetes and progression to microalbuminuria is equivocal. The correlation of duration and urine microalbuminuria is quite clear in type 1 diabetes.

Race

Cowie et al.(74) studied all black (n=470) and white (n=861) patients with end stage renal disease due to diabetes reported to the Michigan Kidney Registry, USA between 1974 and 1983. The incidence of end stage renal disease due to Type 2 diabetes(n=348) was 4.3 (3.36 - 5.25) fold higher($p < 0.0005$) among blacks after adjustment for the higher prevalence of diabetes among blacks.

Pugh et al.(75) assembled a tri-ethnic cohort from all new cases of diabetic ESRD in San Antonio between December 1987 and July 1991 and between December 1988 and July 1991 in the Dallas county, USA. All non-Hispanic whites and African-Americans and a random sample of half of the Mexican-Americans were approached for enrolment. Age adjusted incidence rates were obtained by diabetes type and by ethnic group. The majority of ESRD was caused by Type 2 diabetes (59.5% for non-Hispanic whites, 92.8% for Mexican-Americans and 84.3% for African-American). Mexican-Americans and African-Americans had 9.2 (6.3 - 13.5) and 9.3 (6.2 - 14.0) times higher incidence of treatment for ESRD caused by Type 2 diabetes compared with non-Hispanic whites (both significant at $p<0.00001$). The relative risks of treatment in the two ethnic groups compared to non- Hispanic whites, whilst smaller at

3.8 (2.2 - 6.4) ($p<0.0001$) and 2.5 (1.5 - 4.2) ($p<0.001$) were still significant after age adjustment using the diabetic population as the denominator. This adjusted for the higher underlying prevalence of Type 2 diabetes seen in both the African-American and Mexican-American ethnic groups.

Stephens et al.(76) studied 1,145 patients initiated for treatment for end stage renal disease(ESRD) in South West Ohio, USA during 1983 and 1984 plus 508 patients who had started treatment for ESRD between 1973 and 1984 inclusive. The incidence of ESRD in people with Type 2 diabetes for blacks was 224.4 per 100,000 compared with 46.5 per 100,000 for whites (odds ratio 4.86, 95% CI: 3.65 - 6.47). The relative risk for blacks varied with age, reaching a peak of 6.9 in persons over the age of 65, with diabetes (both types included). Diabetic nephropathy alone was the primary diagnosis considered to be the cause of ESRD in 70 % of those with Type 2 diabetes.

Among people enrolled in three end stage renal disease treatment programmes in the USA, there is evidence of a preponderance of African American and Hispanic peoples. It is not clear whether this represents a true association or whether (for example) the differences reflect previous levels of health care for these groups.

Smoking

In the study by Mattock et al.(53) all patients with Type 2 diabetes attending a diabetes clinic in London in a single year were followed for a minimum of three years and a maximum of seven years. One hundred and forty six patients were eligible for inclusion (no evidence of haematuria, urinary tract infection or clinical albuminuria). Thirty seven patients with microalbuminuria at the baseline examination were then excluded, as the authors were examining influence of smoking upon the development of microalbuminuria (defined as an albumin excretion rate of 20 μg/min in an overnight urine sample). A further nine patients did not attend any of the follow up examinations after three and seven years. Thus follow up data was available for 100 people, either at three years or at seven years. These people were classified as either current smokers or non smokers. Development of microalbuminuria was significantly higher ($p<0.05$) in the current smoker group, with an odds ratio of 3.72 (95% CI: 1.23 - 11.3), after adjustment for age and sex. Smoking was also a significant factor in a

different prospective follow up study. Over 700 people with older onset diabetes, who were free of complications at baseline, were re-examined after 10 years to measure the incidence of proteinuria and the contributing factors (46). In this study the number of pack years was calculated for each of the participants (n=794 at 10 year follow up). Pack years were defined as the number of cigarettes smoked per day, divided by 20, multiplied by the number of years the patient had smoked. Development of proteinuria was defined as an albumin concentration of 0.3 g/l measured by reagent strip. The participants were divided into those on insulin therapy (n=376) and those not on insulin therapy (n=418). In both the insulin group (odds ratio = 1.11; 95% CI: 1.02 - 1.21) and non insulin group (odds ratio = 2.39; 95% CI: 1.32 - 4.32), greater total pack years smoked was significantly associated with greater risk of developing proteinuria ($p<0.05$), after adjustment for other risk factors. Biesenbach et al.(77) evaluated the influence of smoking on the rate of creatinine clearance in 36 people with Type 2 diabetes (16 smokers). The patients had persistent proteinuria (>0.5 g protein in 24h urine) but near normal creatinine clearance (>7.0 ml/min/1.73m2). Taking into account other potential confounding factors such as blood glucose, blood pressure, serum lipids and proteinuria, smoking was significantly associated with the rate of decrease of the creatinine clearance (1.24 compared with 0.99 ml/min/month; $p=0.01$). However, Niskanen et al.(52) did not find an effect for baseline smoking and the subsequent development of microalbuminuria, in their follow up study. In this study one hundred and thirty three people with newly diagnosed diabetes were followed for 10 years. Likewise, whether someone was a smoker or not at study entry did not significantly (at the $p<0.05$ level of significance) predict development of microalbuminuria or proteinuria, in a six year follow up study of people recently diagnosed with Type 2 diabetes by Wirta et al (60). Similarly, in a six year follow up study of 176 people with Type 2 diabetes, Gall et al.(63) did not find a positive history of smoking to be significantly predictive in the development of microalbuminuria (AER =30 – 299 mg/24h) or proteinuria (AER >300 mg/24h). Finally, Sasaki et al.(64) followed 1,196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline.

Smoking was not found to significantly predict the development of Albustix positive albuminuria.

Summary, Evidence that smoking is a predictive factor on the development of microalbuminuria is equivocal(although it is associated with microvascular disease in Type 2 diabetes).

Lipids profile

Gall et al.(63) followed 176 people with Type 2 diabetes with normal albumin excretion rates(AER <30 mg/24h) for approximately 6 years (range 1.5 - 6 years, median 5.8 years). A 1% higher mean serum cholesterol level meant a patient had a relative risk of developing microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER >300 mg/24h) of 1.4 (95%CI: 1.1 - 1.7, p<0.01),after adjustment for other risk factors.

The Beilin et al.(69) study of 666 people with Type 2 diabetes followed people for seven years in a hospital diabetes clinic in Australia. A significant association of log triglyceride with urine albumin levels >30 mg/l was found (p=0.0001) after adjustment for other risk factors. No association was found with HDL or total cholesterol.

Ravid et al.(62) collected follow up data on 574 people with Type 2 diabetes. The participants were drawn from a diabetes clinic in Israel and were followed for between two and nine years (mean 7.8 $\pm$ 0.9). Baseline total cholesterol < 5.25 mmol/l, high density lipoprotein levels (HDL) <1.14 mmol/l and low density lipoprotein (LDL) 3.21 mmol/l were significant determinants of microalbuminuria (albumin excretion rate 30 – 300 mg/24h) in univariate analyses (all p<0.001) with odds ratio = 20.59 (CI 12.67 - 33.45) for cholesterol, 7.76 (CI 5.17 - 11.64) for HDL and 6.24 (CI 4.8 - 13.35) for LDL. After inclusion in a multiple logistic regression model, total cholesterol was a major determinant of the subsequent decline in renal function. The degree of albuminuria was also influenced by HDL values and the risk of microalbuminuria was predicted by initial values of total cholesterol and HDL. Duration to development of microalbuminuria was mainly determined by HDL and two other factors (mean blood pressure and body mass index).

The UKPDS(78) found an association, after adjustment for age, between urine albumin excretion and fasting plasma triglyceride ($p<0.0001$) and fasting plasma LDL cholesterol ($p<0.05$) in 585 patients followed from three months to three years. Patients were initially treated by diet therapy but within three years 65% had been allocated to other therapies. However Mattock et al.(53) measured serum cholesterol and triglycerides in 100 Caucasian patients with Type 2 diabetes at baseline, and then again after three years and seven years. After accounting for other potential risk variables (blood glucose, smoking, blood pressure and urine albumin excretion rate) serum cholesterol or triglycerides did not attain significant levels of effect(at the $p<0.05$ level of significance), in determining the development of microalbuminuria in 29 of the 100 patients.

Wirta et al.(60) recruited 150 people recently diagnosed with Type 2 diabetes. Serum cholesterol was measured at baseline, along with urine albumin excretion rate. Microalbuminuria was defined as an albumin excretion rate of 30 – 300 mg/24 hr and proteinuria as an albumin excretion rate of >300 mg/24 hr. The influence of serum cholesterol upon progression of disease was measured over the follow up period of six years. Progression was defined as microalbuminuria at the end of the study in someone who was normoalbuminuric at baseline, and proteinuria at follow up in someone who was either normoalbuminuric or microalbuminuric at baseline. There was no significant association (at the $p<0.05$ level of significance) between serum cholesterol and progression of albumin excretion rate in the study.

The majority of studies found an association between abnormal lipid profile and increased urine albumin excretion.

Body mass index

Ravid et al.(62) measured the body mass index (BMI) and albumin excretion rate every six months for a mean period of 7.8 years in a cohort of 574 patients who were initially free of abnormal urine albumin levels (albumin excretion rate<30 mg/24hr). In univariate analysis, higher BMI at baseline was found to be significantly predictive of microalbuminuria over the course of the study ($p<0.001$). After adjustment for other risk factors, the degree of albuminuria, duration to the

development of microalbuminuria, and risk for microalbuminuria were all determined by BMI alongside some other variables. However this was the only study to report a significant association between BMI and renal disease

Schmitz et al.(65) followed 278 people with Type 2 diabetes from a clinic in Denmark to assess the influence of BMI on progression of renal disease. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration 15 μg/ml) to microalbuminuria (15 mg/l urinary albumin concentration 200 mg/l) and from microalbuminuria to proteinuria (urinary albumin concentration >200 mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. body mass index was not significantly correlated with progression of albuminuria in 172 patients followed up after four years ($p=0.09$), but was for 135 with six years of data ($p=0.015$), after adjustment for diastolic and systolic blood pressure, plasma glucose, HbA_{1C}, age, sex and baseline albuminuria.

In Niskanen et al.(52) the baseline BMI was measured for 133 people with newly diagnosed Type 2 diabetes. This baseline BMI was not significantly different (at the $p<0.05$ level of significance) in people who developed microalbuminuria (albumin excretion rate >30 mg/24h) after 10 years, compared to those who remained normoalbuminuric.

Wirta et al.(79) did not find a significant effect for BMI at baseline for subsequent development of microalbuminuria (defined as an albumin excretion rate of 30 - 300 mg/24h) or proteinuria(defined as an albumin excretion rate of >300 mg/24h).

Gall et al.(63) assessed BMI at baseline in 176 people with Type 2 diabetes, who were initially free of abnormal albumin excretion rate (AER<30 mg/24h). There was no significant (at the $p<0.05$level) relationship between baseline BMI and development of microalbuminuria (AER = 30 - 299mg/24h) or proteinuria (AER >300 mg/24h).

The evidence of an association between basal BMI and increased albumin excretion is equivocal.

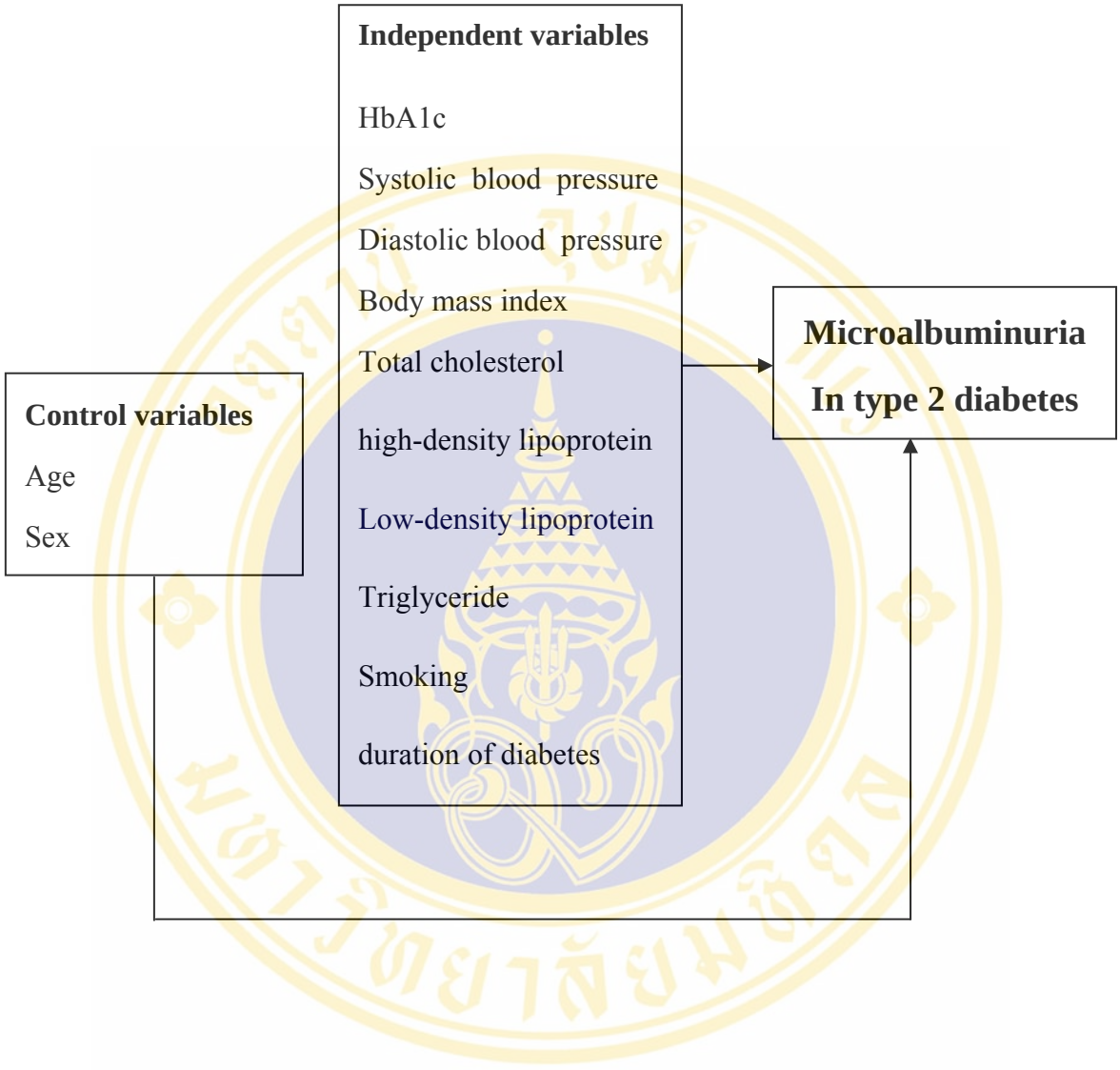

Figure 3. Conceptual Framework

CHAPTER III

METERIALS AND METHODS

This study, there were 2 major objectives. First, to determine prevalence of microalbuminuria in type 2 diabetes. Second to identify risk factors associated with microalbuminuria in Thai type 2 diabetes.

For the primary objective were to determine prevalence of microalbuminuria in type 2 diabetes

Study Design:

Meta-Analysis

General eligibitity of studies.

Studies considered eligible were type 2 diabetes from all settings and available ethnic groups, where quantitative or semi-quantitative measurements of urinary albumin concentration, excretion rate or ratio of urinary albumin to creatinine were reported. Article has to be scale or checklist(see Appendix) designed to assess quality of systemic reviews and meta-analysis.(80, 81, 82)

Literature search

Pubmed: January 1980 - July 2006.

Three independent searches with keywords: microalbuminuria, type 2 diabetes, prevalence , cross-sectional study, meta-analysis, complication.

PubMed “related articles” function to find others.

Data extraction

Checklists and scales assessed for: 1) number of items included in tool; 2) aspects of quality assessed; 3) whether or not article included explicit statement regarding purpose of tool; and 4) time to completion of tool.

Data extraction was completed in a group and consensus reached.

Search results

The PubMed searched yielded a total 80 articles of potential relevance to microalbuminuria or type 2 diabetes. Reasons for exclusion of articles were: cohort study, type 1 diabetes with type 2 diabetes, duplication in national journal. After these exclusions, 16 papers on type 2 diabetes were initially selected.

Characteristics of included studies

The main characteristics of these 16 studies are shown in Table 5. Data were reported from 10,281 patients with type 2 diabetes. The study designed was cross-sectional study both hospital and population based.

Table 5 The main characteristics of 16 article.

Study	Population	Number	study design	Prevalence Rate (%)
Varghese(2000)	South india	1,425	cross-sectional	36.3
TKW Tam(2003)	Hong Kong	1,161	cross-sectional	13.4
Ahmedani MY(2005)	Pakistan	2,100	Multi-center	34.0
Lee KU(1995)	Koreans	631	cross-sectional	20.0
Hashim(2004)	Lahore	150	cross-sectional	46.7
Bruno G(1996)	Italy	1,967	Population-base	32.1
Erasmus(1992)	Nigreria	113	cross-sectional	56.5
Leza-Torres O(2005)	Coahuila	301	cross-sectional	85.3
Annemilke(2006)	Amsterdam	195	cross-sectional	17.2
Mattock(1992)	English	141	cross-sectional	25.0
Dasmahapatra(1994)	African-American	116	cross-sectional	31.0
Alzaid(1994)	Saudi Arabian	184	cross-sectional	41.3

Table 5 The main characteristics of 16 article.(Continued.)

Study	Population	Number	study design	Prevalence Rate (%)
Klein(1984)	American	798	Population-base	26.0
Masoud R.M(2004)	USA	590	cross-sectional	25.9
Onyechi(2000)	Bahraini	312	cross-sectional	25.0
Peera(2005)	Thai(DM&HT)	97	cross-sectional	43.3
Summary	**16 studies**	**10,281**		

The secondary objective were to identify risk factors associated with microalbuminuria in type 2 diabetes.

Study Design:

This research was designed as a hospital-based, multicenter, cross-sectional study.

Study Population

The study population being Type 2 diabetes patients who attended at a diabetic clinics of 11 tertiary centers were registered, between April to December 2003.

Sampling Technique

The Type 2 diabetes patients who attended at a diabetic clinics of 11 tertiary centers were registered during study period and they were randomly sampling on specific inclusion criteria.

Inclusion Criteria

1. The study subjects had fasting blood sugar $\geq$ 126 mg/dl more than two times or OGTT $\geq$ 200 mg/dl.

2. The study subjects are type 2 diabetes.

3. The study subjects are willing to participate and sign the consent form, especially who can answer the question.

Exclusion Criteria

The age of the study subject is below 18

Sample Size

The sample size was calculated based on ability of the study to determine prevalence of microalbuminuria and associated factors of microalbuminuria in type 2 diabetes.

1. Sample size calculation(83) **was based on the estimation information:**

$$n = \frac{Z^2_{\alpha/2} P(1-P)}{e^2}$$

Where n = Sample size

$Z_{\alpha/2}$ = Percentile at (1-α/2)% of standard normal curve in two tailed test with α=0.05(1.96)

P = Estimated event rate of microalbuminuria in type 2 diabetes patients.(15% - 85 %)

e = maximum permissible error(3%)

The sample size was estimated event rate of microalbuminuria in type 2 diabetes patients at 15 to 85 % as follows:

P	1-P	n
0.15	0.85	544.23
0.20	0.80	682.95
0.25	0.75	800.33
0.30	0.70	896.37

P	1-P	n
0.35	0.65	971.07
0.40	0.60	1024.43
0.45	0.55	1056.44
0.50	0.50	1067.11

2. Sample size calculation was based on the logistic regression model(84) (Appendix): Result of fitting a logistic regression model to the southern India data. (Varghese et al.) n= 1,425

Variable	b	S_b	p-value	Odds ratio(95%CI)
Age	0.25	0.06	<0.0001	1.3(1.1 to 1.4)
DBP	**0.43**	**0.08**	**<0.0001**	**1.5(1.3 to 1.8)**
HbA1c	0.29	0.068	<0.0001	1.3(1.2 to 1.5)
FBS	0.23	0.074	0.002	1.3(1.1 to 1.5)
Duration of DM	0.18	0.052	0.005	1.2(1.1 to 1.3)

$$\chi_i^2 = \left(\frac{bi}{s_{bi}}\right)^2 , = \left(\frac{0.43}{0.08}\right)^2 , = 28.89$$

$$R^2 = \frac{\chi_i^2}{\chi_i^2 + n - p - 1} , = \frac{28.89}{28.89 + 1425 - 0.36 - 1} , = 0.0199$$

Parameter	Description	Value	source
P_0	Estimated prevalence of microalbuminuria among type 2 diabetes patient	0.36	Varghese et al.
R^2	Multiple correlation coefficient of the covariate DBP with the remaining covariates(e.g. HbA1c)	0.0199	calculation
$Z_{1-\alpha}$	Percentile at(1-α)% of standard normal curve in two tailed test with α = 0.05	1.645	Determination
Z_β	Percentile at(1-β)% of standard normal curve with β = 0.2	0.842	Determination

$$n = \frac{1 + 2P_0\delta}{1 - R^2} \times \frac{(Z_{1-\alpha} + Z_\beta e^{-0.25\beta_i^{*2}})^2}{P_0\beta_i^{*2}}$$

Where $=[\ln(\text{OR of DBP})]^2 = [\ln(1.5)]^2 = 0.16$

$$\delta = \frac{1+(1+\beta_i^{*2})e^{1.25\beta_i^{*2}}}{1+e^{-0.25\beta_i^{*2}}} = 1.24$$

$$n = \frac{(1+2*0.36*1.24)}{1-0.0199} \times \frac{(1.645+0.842\times e^{-0.25(0.16)})^2}{0.36\times 0.16} = 197$$

3. Sample size calculation was based on testing hypothesis for comparison of two proportions. Result of test hypothesis to the southern India data.(Varghese et al.) n= 1,425

Parameter	Description	Value	source
P_1	Estimated prevalence of microalbuminuria among type 2 diabetes patient	0.36	A. Varghese et al.
P_2	The probabilities of exposure given disease absence	0.46	
$Z_{1-\alpha}$	Percentile at(1-α)% of standard normal curve in two tailed test with α = 0.05	1.645	Determination
Z_β	Percentile at(1-β)% of standard normal curve with β = 0.2	0.842	Determination

$$p_2 = \frac{p_1(OR)}{1-p_1+(OR)p_1} = 0.46$$

$$p = \frac{p_1+p_2}{2} = 0.41$$

$$n_1 = \frac{\left[Z_{\alpha/2}\sqrt{2p(1-p)} + Z_\beta\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2} = 409.74$$

Corrections n_p for p covariates of logistic regression(85)

$$n_p = \frac{n_1}{1-R^2}$$

The minimize sample size was 1,025.

R square	n_p
0.3	585.3
0.4	682.9
0.5	819.5
0.6	1024.3

Summary:

Sample size calculation was based on the estimation, n = 1,068

Sample size calculation was based on the logistic regression model, n = 197

Sample size calculation was based on testing hypothesis for comparison of two proportions, n = 1,025

Then, the least number of subjects required in this study become 1,068 subjects.

Instruments

The data were collected from medical record and interview. The case record form was created by researcher team and biostatistician. It is divided into 4 sections(see Appendix) as follow:

Section 1 Demography: gender, birthday, occupation, education, right to pay and home-address, fill data by research nurse

Section 2 Medical history: date of diagnosis and diagnosis fill data by endocrinologist

Section 3 Monitoring data(Risk and Complications): height, weight, systolic blood pressure, diastolic blood pressure, blood chemistry were fill data research nurse and endocrinologist were fill in topics of complication.

Section 4 Medications: hypoglycemic agent(insulin, sulfonylurea, glinide, metformin, TZD, A-GI), Anti-hypertension drug(ACE-I, ARB, B-blocker, A-blocker,

CCB, Diuretic), Anti dislipidemia drug(statin, firbrate, ASA) and history of herbal used,fill data by endocrinologist

Data Collection in diabetes registry project

1. Workshop on training the researcher and research nurse for data collection

2. The researcher and research nurse used a case record form to interview and physical examination for complications screening and laboratory results the study subjects at diabetic clinic.

3. The Investigator of each site to correct the data then to sign name and date in case record form.

4. The research nurse sent the case record form to research coordinator.

5. Research coordinator completes case record form and the data entry to the database is performed by some clerks.

6. Blood Pressure was measured by Automatic Blood Pressure(OMRON)

7. Laboratory was collected from medical record

8. Complication was collected from medical record and examination

For the current analysis, the authors restricted data to include only type 2 diabetes patients from Diabetes Registry Project. Available for analysis is 1,734, all of which had completed standard method and criteria for diagnosis of albuminuric stage.(Figure 4.)

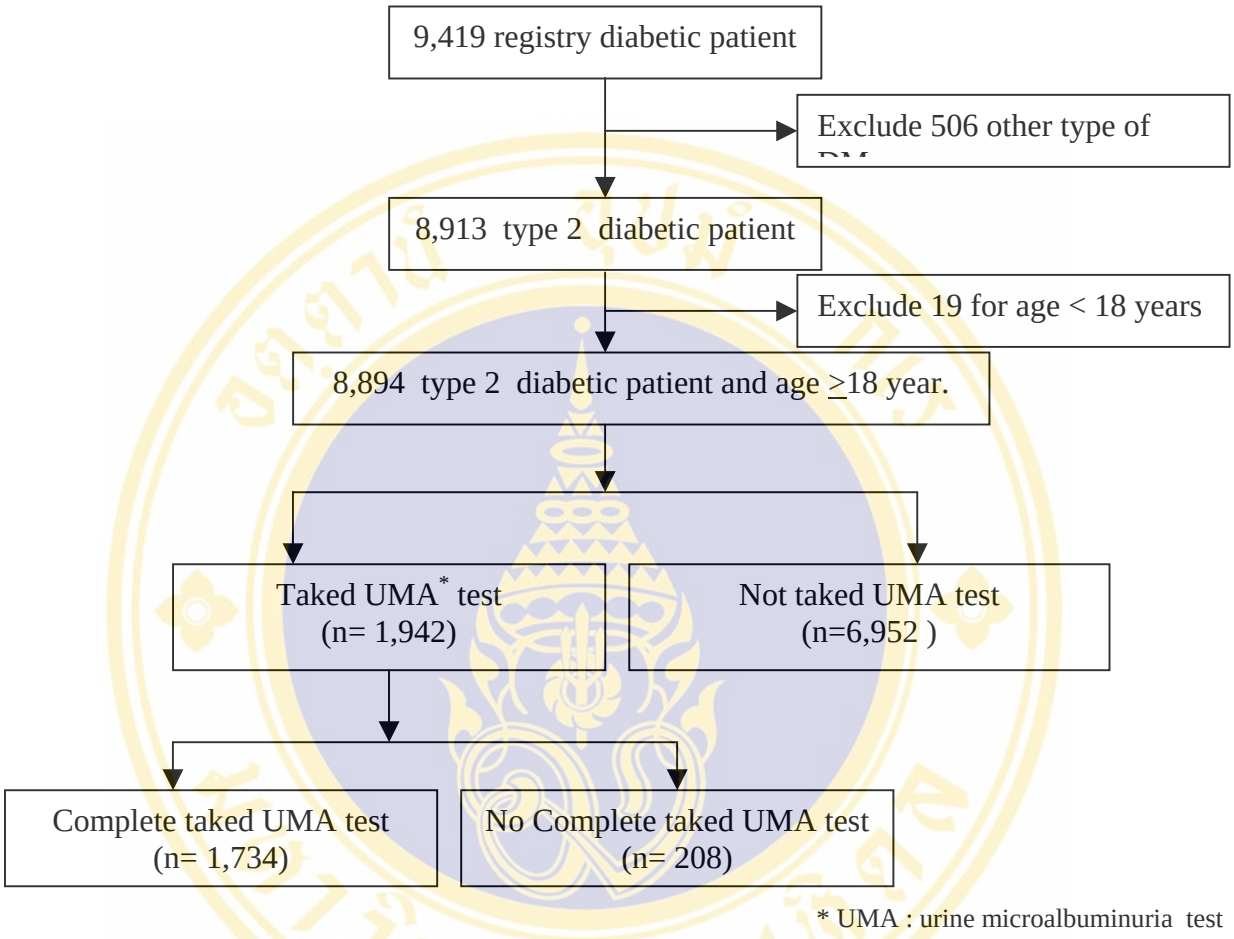

Figure 4. Patient classification.

Ethical Consideration

1. This study was approved by 11 ethical committees at Rajavithi Hospital, Chulalongkorn Hospital, Maharat Nakhon Ratchasima Hospital, Theptarin General Hospital, Phramongkutklao Hospital & Medical College, Ramathibodi Hospital, Maharat Nakhon Chiang Mai Hospital, Siriraj Hospital, Prince of Songkhla University,Bangkok Metropolitan medical college and Vajira Hospital and Khon-Kaen University.

2. All patients had an explanation about objective, method, significant of this study from the research nurse and researcher until they were cleared and had willing to participate in this study. The willing study subjects signed up the consent form.

Data Analysis

1. Descriptive statistics such as frequency, percent, mean and standard deviation will be used to describe the studies subjects.

2. Prevalence of microalbuminuria was estimated from cross-sectional surveys. The combined prevalence was calculated as a weighted mean of prevalence from each individual study with 95% confidence interval(see Appendix).

Step 1: Heterogeneity between studies was tested using the chi-square test with k-1 degrees of freedom where k is the number of articles.

Step 2: Calculation Q statistic .

All analysis for Meta Analysis was carried out using Excel.

3. Analytic statistics:

Proportions of studied variables were compared with Chi-square test.

Univariate analysis was used to define each associated factor with microalbuminuria by calculating the odds ratio(crude OR) and 95% confidence interval of crude odds ratio.

Logistic regression was used to calculate odd ratios for microalbuminuria after controlling for multiple covariates simultaneously.

All statistical analyses were completed with STATA 8.0

CHAPTER IV

RESULTS

Data collection was conducted from Diabetes Registry Project. The total number of the type 2 diabetes was 8,894. According to Table 6 show that the patient who had had detected microalbuminuria 1 times was 21.8% but if complete detected microalbuminuria was 19.5%. This research has selected only three times diagnosed patients into the field. From the data of Diabetes Registry Project, we found the prevalence of microalbuminuria in Thai type 2 diabetes patients was 53.4%, 926 of 1,734 subjects.

Table 6 Screening and prevalence of microalbuminuria in diabetes registry.

Screening and prevalence	Yes n(%)	No n(%)	Total
Microalbuminuria screening (more or equl 1 time)	1,942(21.8)	6,952(78.2)	8,894
Microalbuminuria screening (complete 3 time)	1,734(19.5)	7,160(80.5)	8,894
Prevalence of Microalbuminuria	926(53.4)	808(46.6)	1,734

Prevalence of microalbuminuria in type 2 diabetes

The Meta Analysis gave an overall prevalence rate of 35.9%(95%CI 27.9 to 43.9) in the 17 studies(16 papers were initially selected and the data of Diabetes Registry Project) which possible to calculate baseline prevalence(Table 7). There was significant heterogeneity between studies.(P-value = 0.028)

Table 7 Meta-analysis of findings on the cumulative prevalence of microalbuminuria in patients with type 2 diabetes.

Study	Population	Number	study design	Prevalence Rate(%)	95%CI	
					Lower	Upper
Varghese(2000)	South india	1,425	cross-sectional	36.3	33.8	38.8
TKW Tam(2003)	Hong Kong	1,161	cross-sectional	13.4	11.5	15.5
Ahmedani MY(2005)	Pakistan	2,100	Multi-center	34.0	31.9	36.1
Lee KU(1995)	Koreans	631	cross-sectional	20.0	16.9	23.3
Hashim(2004)	Lahore	150	cross-sectional	46.7	38.5	55.0
Bruno G(1996)	Italy	1,967	Population-base	32.1	30.0	34.2
Erasmus(1992)	Nigreria	113	cross-sectional	56.5	47.0	65.9
Leza-Torres O(2005)	Coahuila	301	cross-sectional	85.3	80.9	89.2
Annemilke(2006)	Amsterdam	195	cross-sectional	17.2	12.4	23.5
Mattock(1992)	English	141	cross-sectional	25.0	17.9	32.8
Dasmahapatra(1994)	African-American	116	cross-sectional	31.0	22.8	40.3
Alzaid(1994)	Saudi Arabian	184	cross-sectional	41.3	34.1	48.8
Klein(1984)	American	798	Population-base	26.0	22.9	29.1
Masoud R.M(2004)	USA	590	cross-sectional	25.9	22.4	29.7
Onyechi(2000)	Bahraini	312	cross-sectional	25.0	20.3	30.2
Peera(2005)	Thai(DM&HT)	97	cross-sectional	43.3	33.3	53.7
DRP(2003)	Thai	1,742	Multi-center	53.4	51.0	55.8
Meta Analysis	**17 studies**	**12,023**		**35.9**	**27.9**	**43.9**

Heterogeneity chi-square = 1538.4 df(16), P-value = 0.028)

The prevalence rate and confidence intervals for 17 studies as reported in Table 7, are plotted in Figure 5. This plot showed the difference in prevalence rate between estimates from different studies.

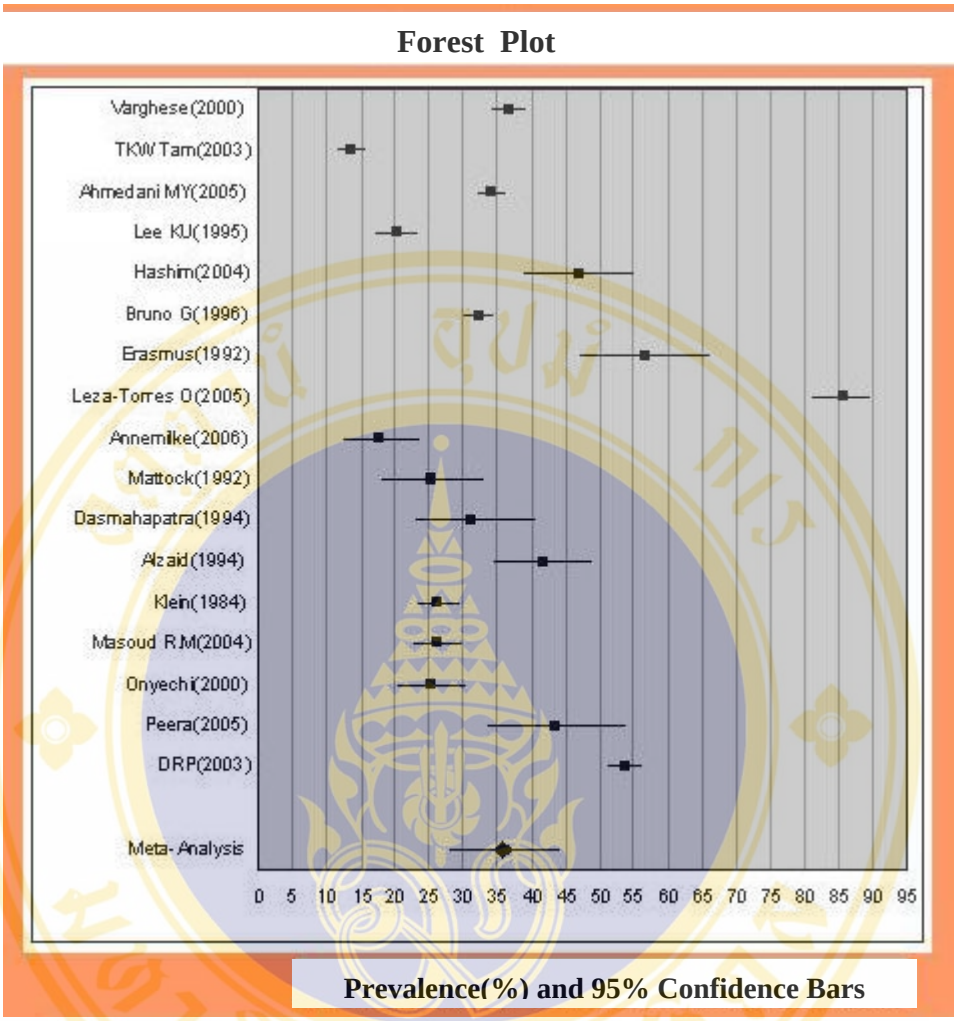

Figure 5. Forest plot for the prevalence of microalbuminuria in type 2 diabetes.

General Characteristics of the Samples

Demographic data of the subject were shown in Table 8 could be described in each factor as follows.

Gender, This study found that the type 2 diabetes male patients, who were on the microalbuminuria, amount to 344 of 593 persons, or 58.0%. While the female patients, who were on the microalbuminuria, amount to 582 of 1,141 persons, or 51.0%. In group of microalbuminuria patient, there were female(62.9%) and male(37.1%). The differences in the gender distribution between with and without microalbuminuria is significant. (P-value = 0.006).

Age, patients who were over 70 years old, were amount to 220 of 379 persons (58.0%) found the microalbuminuria, 60-69 years old patients were found amount to 307 of 574 persons(53.5%), 50-59 years old patients were found amount to 255 of 513 persons(49.7%), 40-49 years old patients were found amount to 114 of 211 persons (54.0%), and 30-39 years old patients were found amount to 26 of 50 persons (52.0%), which almost all age group were found over 50%; nevertheless, the age were not significant difference between group of microalbuminuria (P-value = 0.286).

Educational levels, persons who were educated higher than bachelor degree, were amounted to 39 of 60 persons (65.0%) found the microalbuminuria. While persons who were no educated are found amount to 102 of 158 persons(64.6%). The differences in the education distribution between with and without microalbuminuria is significant.(P-value = 0.007).

Occupation, Most of the samples in both with and without microalbuminuria groups were no occupation with 39.2% and 45.3%, respectively. Skill occupation showed the lowest percentage in both without microalbuminuria(5.6%) and with microalbuminuria(8.6%). There was significant between with and without microalbuminuria(P-value = 0.001). In skill occupation patients were found the microalbuminuria , amount to 80 of 125 persons, or 64%. The next below was no-occupation patients found 419 of 736 persons(56.9%), and housewife occupation found 175 of 368 persons(47.6%).

Table 8 Characteristic of the Samples

Characteristic	n	Without MA n(%)	MA* n(%)	P - value
Sex				0.006 [a]
Male	593	249(42.0)	344(58.0)	
Female	1,141	559(49.0)	582(51.0)	
Age (years)				0.286[a]
< 30	7	3(42.9)	4(57.1)	
30 – 39	50	24(48.0)	26(52.0)	
40 – 49	211	97(46.0)	114(54.0)	
50 – 59	513	258(50.3)	255(49.7)	
60 – 69	574	267(46.5)	307(53.5)	
≥ 70	379	159(42.0)	220(58.0)	
Education				0.007 [a]
No schooling	158	56(35.4)	102(64.6)	
Primary school	706	329(46.6)	377(53.4)	
Secondary school	504	250(49.6)	254(50.4)	
Bachelor degree	306	152(49.7)	154(50.3)	
High than bachelor degree	60	21(35.0)	39(65.0)	
Occupation				0.001[a]
No occupation	736	317(43.1)	419(56.9)	
Labor force	215	102(47.4)	113(52.6)	
House wife	368	193(52.2)	175(47.6)	
Skill	125	45(36.0)	80(64.0)	
Profession	290	151(52.1)	139(47.9)	

[*] MA: Microalbuminuria

[a] Pearson chi-square test

Factors association of microalbuminuria in type 2 diabetes.

Smoking, The patients who were current smoking or had ever smoked amount to 350 persons, it found that 212 persons(60.6%) have the microalbuminuria, while the amount to 714 persons(51.6%), of the non smoking patients amount to 1,384 persons, had the state. It was also found that the smoking correlate to the microalbuminuria state statistic significantly (P-value= 0.003)(Table 9).

Alcohol drinking, patients who were current drinking or had ever drank amount to 339 persons, it found that 191 persons(56.3%) had the microalbuminuria state, the amount to 735 persons(52.7%), of the non drinking patients amount to 1,395 persons, had the state. Most of the samples in both without and with microalbuminuria groups were never alcohol drinking with 81.7% and 79.4%, respectively. It was also found that the alcohol consumption had no significant difference between without and with microalbuminuria(P-value= 0.226) (Table 9).

Table 9 Comparison of behavioral factors between not and microalbuminuria groups.

Factors	n	Without MA n(%)	MA n(%)	P - value
Smoking				0.007 [a]
Never	1384	670(48.4)	714(51.6)	
Ever/current	350	138(39.4)	212(60.6)	
Alcohol				0.174 [a]
Never	1395	660(47.3)	735(52.7)	
current / Abstinece	339	148(43.7)	191(56.3)	

[a] Pearson chi-square test

Table 10 Mean(SD) values of baseline variables in type 2 diabetes.

Factors	Without MA mean(SD)	MA mean(SD)	Total mean(SD)	Mean diff & 95%CI	P-value [b]
Age	60.5(10.6)	61.5(11.1)	61.0(10.9)	-1.1(-2.1 to –0.1)	0.039
FBS	155.4(49.5)	158.2(56.0)	156.9(53.1)	-2.8 (-7.8 to - 2.2)	0.269
Hba1c	7.9(1.6)	8.3(1.9)	8.1(1.8)	-0.4 (-0.6 to –0.3)	< 0.001
Creatinine	1.0(0.6)	1.1(0.6)	1.1(0.6)	-0.1 (-0.2 to –0.09)	< 0.001
Total cholesterol	196.8(37)	195.2(41.7)	195.9(39.6)	1.6 (-2.2 to 5.3)	0.4073
HDL - C	58.2(14.5)	53.6(14.3)	55.7(14.6)	4.6 (3.2 to 6.0)	<0.001
LDL - C	110.7(31.6)	112.3(35.9)	111.5(33.9)	-1.6 (-4.9 to 1.59)	0.3193
Triglyceride	146.5(80)	153.1(100.5)	150.0(91.7)	-6.6 (-15.2 to 2.0)	0.1322
Systolic BP	141.1(19.6)	147.5(22.3)	144.5(21.3)	-6.3 (-8.3 to –4.4)	<0.001
Diastolic BP	79.2(11.0)	79.6(11.7)	79.4(11.4)	-0.4 (-1.5 to 0.7)	0.4650
BMI	25.5(4.0)	26.1(4.3)	25.8(4.2)	-0.7 (-1.1 to –0.3)	0.0012
Age of onset	50.8(10.9)	49.5(12.1)	50.1(11.6)	1.3 (0.2 to 2.4)	0.0187
duration of diabetes	9.7(7.7)	12(9.1)	10.9(8.5)	-2.4 (-3.2 to-1.6)	<0.001

[b] Independent t-test

According to Table 10, The mean age was 61.0±10.9%, fasting plasma glucose was 156.9±53.1 %, with a mean glycosylated haemoglobin(HbA1c) of 8.1±1.8 %. A mean creatinine level of 1.1±0.6 mg/dl. A mean Total cholesterol of 195.9+39.6 mg/dl., a mean triglyceride of 150±91.7 mg/dl and mean of HDL-C and LDL-C were 55.7±14.6 and 111.5±33.9 mg/dl, respectively.

The mean systolic blood pressure and diastolic blood pressure were 144.5±21.3 and 79.4±11.4 mmHg, respectively.

The mean age of onset of diabetes was 50.1±11.6 years, and a mean duration of diabetes was 10.9±8.5 years.

Table 10 showed the mean of Age, HbA1C, Creatinine, HDL-C, Systolic Blood Pressure, Body Mass Index, Age of onset and duration of diabetes, were significantly between without and with microalbuminuria(P-value less than 0.05).

The association and effect of various factors and microalbuminuria in type 2 diabetes.

Table 11 showed the univariate analysis among pontential risk factors and microalbuminuria. The detail were as follows:

HbA1C, The patients who had hbA1c more or equal 7% had the risk to the microalbuminuria state occurrence at 1.43 times of ones have it less than 7% (95% CI of crude OR 1.15 to1.78; P-value = 0.001)

Systolic blood pressure(SBP), The patients who had Systolic Blood Pressure equal or greater than 130 mmHg had the risk to the microalbuminuria state occurrence at 1.35 times of ones had it less than 130 mmHg (95% CI of crude OR 1.07 to 1.69; P-value = 0.008)

HDL-C, The patients who had HDL less than 40 mg/dl (male) or 50 mg/dl (female) had the risk to the microalbuminuria state occurrence at 1.48 times of ones had it equal or greater than 40 mg/dl(male)or 50 mg/dl(female), respectively (95% CI of crude OR 1.12 to 1.95; P-value = 0.004)

Duration of diabetes, The patients who had duration of diabetes of more or equal 20 years had the risk to the microalbuminuria occurrence at 2.08 times of ones had duration of diabetes less than 5 years (95% CI of crude OR 1.48 to 2.94; P-value < 0.001) The risk of microalbuminuria occurrence was tends to increase by the duration of diabetes. The patients, who had duration of diabetes for 10-14.9, 15-19.5,

and 20 years, had the risk to the microalbuminuria occurrence were 1.88, 2.33, and 2.28 times respectively, of ones had duration of diabetes less than 5 years (95% CI of crude OR 1.44 to 2.51; P-value < 0.001, 1.64 to 3.31; P-value < 0.001, 1.48 to 2.94; P-value < 0.001, respectively). But found that the patients who had duration of diabetes between 5-9.9 years, had the risk to the microalbuminuria occurrence at 1.38 times of patients who had duration of diabetes sick less than 5 years, but had not statistic significantly (95% CI of Crude OR 1.05 to 1.80; P-value = 0.0157)

Smoking, Type 2 diabetes subject with smoking had a higher risk of microalbuminuria than those of non smoking (95% CI of Crude OR 1.13 to 1.85; P-value = 0.003).

Body mass index, The patients with body mass index between 25-29.9 kg/m^2 and more or equal 30 kg/m^2 was significant (OR = 1.46, 95% CI of crude OR 1.13 to 1.88; P-value = 0.003 and OR = 1.71, 95%CI of crude OR 1.24 to 2.37; P-value< 0.001).

Other variables such as, Fasting blood sugar, diastolic blood pressure, LDL-C, Alcohol, Triglycerides did not show significant association with microalbuminuria.

Table 11 Association factors with microalbuminuria unadjust for variables.

Factors	n	Without MA	MA	OR(95% CI)	P value[a]
FBS (mg/dl)					
< 130	552	239(29.6)	313(33.8)	1	0.059
≥ 130	1,182	569(70.4)	613(66.2)	0.8(0.67 – 1.01)	
Hba1c (%)					
< 7	471	250(30.9)	221(23.9)	1	0.001
≥ 7	1,263	558(69.1)	705(76.1)	1.43(1.15-1.78)	
SBP (mmHg)					
< 130	413	216(26.7)	197(21.3)	1	0.008
≥ 130	1,321	592(73.3)	729(78.7)	1.35(1.07-1.69)	
DBP (mmHg)					
< 80	890	417(51.6)	473(51.1)	1	0.826
≥ 80	844	391(48.4)	453(48.9)	1.02(0.84-1.24)	
Total cholesterol					
< 200	963	428(53.0)	535(57.8)	1	0.05
≥ 200	771	380(47.0)	391(42.2)	0.82(0.68-1.0)	
Triglycerides					
≤ 150	1,065	502(62.1)	563(60.8)	1	0.571
> 150	669	306(37.9)	363(39.2)	1.06(0.87-1.29)	
HDL-C					
≥ 40(men), ≥ 50 (women)	498	224(59.9)	274(50.3)	1	0.004
< 40(men), < 50 (women)	421	150(40.1)	271(49.7)	1.48(1.12-1.95)	

[a] Pearson chi-square test

Table 11 Association factors with microalbuminuria unadjust for variables. (Continued.)

Factors	n	Without MA	MA	OR(95% CI)	P value[a]
LDL-C					
≤ 100	686	326(40.4)	360(38.9)	1	0.532
> 100	1,048	482(59.6)	566(61.1)	1.06(0.87-1.30)	
Duration of DM					
< 5	434	248(30.7)	186(20.1)	1	
5- 9.9	484	238(29.4)	246(26.6)	1.38(1.05-1.80)	0.0157
10- 14.9	376	156(19.3)	220(23.8)	1.88(1.41-2.51)	<0.001
15 – 19.9	217	79(9.8)	138(14.9)	2.33(1.64-3.31)	<0.001
≥ 20	223	87(10.8)	136(14.7)	2.08(1.48-2.94)	<0.001
Smoking					
No	1,384	670(82.9)	714(77.1)	1	0.003
Ever/current	350	138(17.1)	212(22.9)	1.44(1.13-1.85)	
Alcohol					
No	1,395	660(81.7)	735(79.4)	1	0.226
Ever/current	339	148(18.3)	191(20.6)	1.16(0.91-1.48)	
BMI					
18.5 – 22.9(normal)	409	217(26.9)	192(20.7)	1	
< 18.5 (low-weight)	27	15(1.9)	12(1.3)	0.9(0.38-2.13)	0.801
23 – 24.9(at risk)	353	174(21.5)	179(19.3)	1.16(0.87-1.56)	0.288
25 – 29.9(obese1)	681	297(36.7)	384(41.5)	1.46(1.13-1.88)	0.003
≥ 30(obese2)	264	105(13.0)	159(17.2)	1.71(1.24-2.37)	<0.001

[a] Pearson chi-square test

The effect of various factors and microalbuminuria by logistic regression analysis

After performing the crude analysis, the factors considers to be significantly associated with microalbuminuria were HbA1c, systolic blood pressure, HDL-C, duration of diabetes, smoking and body mass index.

This association might be influenced by confounding factors. In order to get rid of the potential confounders, Sequential logistic regression was provided by controlling for effects of sex, age, HbA1c, systolic blood pressure, HDL-C, duration of diabetes, smoking and body mass index.

The researcher has investigate effect of some variables, none have been found to be significant effect modifier and not multicolonearity.

After controlling for confounding factors there were 6 risk factors. Namely HbA1c, systolic blood pressure, HDL-C, duration of diabetes, smoking and body mass index, significantly associated with microalbuminuria was shown as follows(Table 12)

Systolic Blood Pressure, The systolic blood pressure equal or greater than 130 mmHg had the risk to the microalbuminuria occurrence at 1.57 times of ones had less than 130 mmHg (95% CI of Adjusted OR 1.13 to 2.17; P-value = 0.007)

HDL less than 40 mg/dl(male) or 50 mg/dl(female) had the risk to the microalbuminuria occurrence at 2.53 times of ones had equal or greater than 40 mg/dl (male) or 50 mg/dl(female), respectively. (95% CI of Adjusted OR 1.52 to 4.22; P-value < 0.001)

Duration of diabetes at 5-99, 10-14.9, 15-19.9, and equal or greater than 20 years, had the risk to the microalbuminuria occurrence at 1.59, 2.38, 3.21, and 2.17 times of ones had less than 5 years, respectively. (95% CI of Adjusted OR 1.08 to 2.35; P-value = 0.020, 1.53 to 3.63; P-value < 0.001, 1.95 to 5.31; P-value < 0.001, and 1.31 to 3.57; P-value = 0.002, respectively)

Smoking, The patient who were current or ever smoking, had the risk to the microalbuminuria occurrence 1.42 times of ones had not. (95% CI of Adjusted OR 1.03 to1.96; P-value = 0.035)

Body mass index, The association between microalbuminuria and body mass index more or equal 30 kg/m^2 had the risk to the microalbumminuria occurrence at 2.08 times of normal persons(18.5- 22.9 kg/m^2) (95% CI of Adjusted OR 1.27 to 3.41; P-value = 0.003)

Table 12 Association between risk factors and microalbuminuria adjusting for sex, age and other variables simultaneously

Factors	Crude OR	95% CI of Crude OR	Adjust OR[C]	95% CI of Adjust OR	P value
Sex					
Male	1		1		
Female	0.75	0.61 – 0.93	0.62	0.36 – 1.07	0.084
Age (years)					
< 30	1		1		
30 – 39	0.81	0.16-4.01	0.49	0.07 – 3.29	0.464
40 – 49	0.88	0.19-4.04	0.57	0.09 – 3.32	0.534
50 – 59	0.74	0.16-3.35	0.52	0.09 – 2.97	0.463
60 – 69	0.86	0.19-3.89	0.54	0.09 – 3.12	0.494
≥ 70	1.04	0.23-4.70	0.69	0.12-3.99	0.678
Hba1c (%)					
< 7	1		1		
≥ 7	1.43	1.15-1.78	1.32	0.97 – 1.81	0.080

Table 12 Association between risk factors and microalbuminuria adjusting for sex, age and other variables simultaneously (Continued.)

Factors	Crude OR	95% CI of Crude OR	Adjust OR[C]	95% CI of Adjust OR	P value
SBP (mmHg)					
< 130	1		1		
≥ 130	1.35	1.07-1.69	1.51	1.13 – 2.16	0.007
HDL-C (mg/dl)					
≥ 40(men), ≥ 50 (women)	1		1		
< 40(men),< 50 (women)	1.48	1.12 – 1.95	2.52	1.52- 4.21	<0.001
Duration of DM (years)					
< 5	1		1		
5- 9.9	1.38	1.05-1.80	1.59	1.08-2.34	0.020
10- 14.9	1.88	1.41-2.51	2.38	1.56-3.64	<0.001
15 – 19.9	2.33	1.64-3.31	3.21	1.95-5.31	<0.001
≥ 20	2.08	1.48-2.94	2.17	1.32-3.57	0.002
Smoking					
No	1		1		
Ever/current	1.44	1.13-1.85	1.42	1.03-1.96	0.034
BMI (kg/m^2)					
18.5 – 22.9 (normal)	1		1		
< 18.5 (low-weight)	0.9	(0.38-2.13)	1.09	0.34-3.29	0.922
23 – 24.9 (at risk)	1.16	(0.87-1.56)	1.18	0.78-1.77	0.438
25 – 29.9 (obese1)	1.46	(1.13-1.88)	1.57	1.09-2.27	0.014
≥ 30 (obese2)	1.71	(1.24-2.37)	2.09	1.28-3.42	0.003

[C] adjusted for age, sex, Hba1c, Systolic blood pressure, HDL-C, duration of DM, smoking, body mass index.

The analysis using sequential logistic regression modelling(Table 13) applied to these data yields the following results for 2 model:

1. Reduce Model* :

$$\text{logit } P(x) = a + b_1(\text{AGE}) + b_2(\text{SEX})$$

logit P(x) = -0.2329+0.0091(AGE)-0.2848(SEX)

2. Full Model** :

$$\text{logit } P(x) = a + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 + b_5x_5 + b_6x_6 + b_ix_i$$

logit P(x) = -2.103+0.002(AGE)-0.063(SEX)+0.229(HbA1c)+0.011(SBP)-0.020(HDL_C)+0.034(duration of dm)+ 0.246(smoke)+0.045(BMI).

Table 13 The effects of risk factors on microalbuminuria adjusting for sex, age.

Factors	Coefficient	Adjust OR	95% CI of Adjust OR	P value
Age	0.002	1.00	0.99-1.01	0.45
Sex	-0.063	0.91	0.71-1.19	0.50
HbA1c	0.229	1.12	1.05-1.18	<0.001
SBP	0.011	1.01	1.00-1.02	<0.001
HDL-C	-0.020	0.98	0.97-0.99	<0.001
Duration of DM	0.034	1.03	1.02-1.05	<0.001
Smoke	0.246	1.27	0.94-1.72	0.12
BMI	0.045	1.04	1.01-1.07	<0.001
Cons	-2.103			

*Logistic model for MA, goodness of fit test, Pearson chi-square= 1505.84, df(1525) , P-value= 0.6040
**Logistic model for MA, goodness of fit test, Pearson chi-square= 1649.6, df(1640) , P-value= 0.4290

CHAPTER V

DISCUSSION

Diabetes Registry Project is the large multi-center epidemiological study conducted in Thailand to determine the epidemiology and diabetes complication in diabetes patient. This sub-analysis with type 2 diabetes, the results will be discussed following the examined in the study.

Discussion on study design

The study is designed as a cross-sectional study. The data were collected in a limited period of time and the outcome was measured only once. Therefore, the association between exposure and outcome could not be summarized. Some other microalbuminuria risk factors, such as menopause, body surface area, diabetic complication, were not covered here; however, they are covered by ongoing studies that investigate the clinical progress of the microalbuminuria cohort, stratified by duration of diabetes, glycaemic control, and treatment with angiotensin-converting enzyme inhibitor.

The meta analysis techniques were helpful in explaining a significant portion of the observed variation in microalbuminuria prevalence rates. In meta analysis study has limitations. The analysis focuses on a subgroup of studies selected from a larger review. The search strategy for large review, however comprehensive, did not specifically target, and therefore, some relevant studies may have been missed.

In this study, the type 2 diabetes were selected from data of Diabetes Registry Project, which they had be diagnosed by same standard method, this can minimized selection bias. Blood pressure was measured twice, at least 1 minute apart, by

automated blood pressure machine(Omron T4). Urinary albumin levels can vary widely from sample to sample in the same patient, Factor that can increase urinary albumin excretion include urinary tract infection, exercise, fever. By collection data from test microalbuminuria 3 times can reduce bias form effect of infection, fever and exercise.

A limitation of this study, Laboratory results reported in the registry were collected from routine examinations of the institutes'clinical care which had been tested with past 6 months or in the following 3 months after registration. These are more likely chance of occurring measurement bias. The other of limitations of this study is that it is a clinical based study. This could have introduced some degree of referral bias.

However, the data can still be used to solve health problems and to be used as the data for future studies.

Discussion on study results.

Microalbuminuria

The Centers for Disease Control and Prevention(CDC) recommend early detection of microalbuminuria in patients with diabetes(86). This study to showed the type 2 diabetes who had microalbuminuria screening only 21.8% among all type 2 diabetes patients, which is a high loss of early detection of microalbuminuria in Thai type 2 diabetic patients.

Preventing the development of microalbuminuria is a key treatment goal for reno-protection and cardioprotection(87,88). Microalbuminuria is predictive of adverse events in diabetes and might be a useful screening tool to help to target treatment more effectively. Several studies document that microalbuminuria can be reduced by treatment with block the rennin angiotensin drug. The early detection of microalbuminuria and early control of diabetes retards the development of structural changes in early diabetic complication. The American Diabetes Association also

recommended annual testing for microalbuminuria for persons who have diabetes for five years or more(89). Awareness of microalbuminuria can assist the clinician in identifying diabetic patients at high risk for both micro-and macrovascular complication.

In this study, The researcher measured microalbuminuria to be qualitative data. However, testing for microalbuminuria in a timed sample of urine using the double antibody radioimmunoassay(RIA) method(quantitative data) is cumbersome and requires special laboratory facilities. Quantitative ways of determining urinary concentrations of very small amounts of albumin which have high sensitivity and specificity. Leong So et al.(90) suggest that Micral test with either the first morning or random urine specimen offers a simple, reliable, rapid and convenient method for screening for microalbuminuria in the diabetic patient.

The prevalence of microalbuminuria was 53.4%. The prevalence of microalbuminuria was much higher than rates of 43.3% reported from Thai patients with type 2 diabetes and hypertension in Peera studies(91), and higher than the mean of 35.9% reported from the Meta Analysis. The prevalence of microalbuminuria was about 13% in Japanese cohort(92). The variation in rate could be as a result of different methods used in those studies, the population and races involved, or variation in standard of care and several methods were used to detect microalbuminuria. It is clear, in this study and others, that microalbuminuria is quite prevalent among patients with diabetes. This obviates the necessity for early detection and treatment.

Microalbuminuria is a useful predictor of renal failure and cardiovascular disease in patients with diabetes, and even an independent predictor of mortality in type 2 diabetes.(93)

Gender

In this study, The type 2 diabetes male and female patients who were on the microalbuminuria 58% and 51% respectively(Table 8). This study supported the

evidence is equivocal that male sex has an increased association with Increased albumin excretion. In the Gubbio cohort(70), risk for microalbuminuria was greater for male than for female. This could reflect an influence of sex hormones on glomerular functions.

Education

This analysis at one point in time showed that education level were related to microalbuminuria could not be accounted for statistical. These data suggested that the persons who were educated high than bachelor degree and no education presence the same prevalence of microalbuminuria.

Hyperglycemia

High blood glucose level are known as a result in thickening of the vascular basement membrane(94). Hyperglycemia is an important determinant for the development of proteinuria in patients with type 2 diabetes. Effective glycaemic control has been shown to prevent the development of complication of diabetes. However, as evidenced by the mean HbA1c of 8.1%(SD.=1.8), the majority of patients in the present study did not achieve optimal glycaemic control.

Many studies suggested a relationship between hyperglycemia and microalbuminuria, cross-sectional study and cohort study(7,10,11,91,93,100).

In this study, the fasting blood sugar of equal or more than 130 mg/dl had not significant association with microalbuminuria(OR = 0.8, 95%CI 0.67 to 1.01, p-value = 0.059). Glycosylated hemoglobin(A1c) of more or equal 7 % was found to be significantly associated microalbuminuria(OR = 1.43, 95%CI 1.15 to1.78, P-value = 0.001)(Table 11) but after adjusting for the effect of other variables it was not significant(OR = 1.32, 95%CI 0.97 to 1.81, P-value = 0.080)(Table 12)

Both HbA1c and fasting blood sugar were not significantly associated with microalbuminuria. So far, it is not known whether glycated hemoglobin is a better tool to investigate risk of microalbuminuria than a single blood glucose determination. Although, HbA1c has been proven as an acceptable method to determine the degree of hyperglycemic because it provides an integrated measure of blood glucose level over the previous 3 months and is not effected by time of day, recent activity, food intake and other factor(95,96). By contrast, a single plasma glucose determination may be influenced by age, activity level, metabolic stress(97). However, Leza-Torres et al.(49) showed that the prevalence of microalbuminuria was 85.3%. It is greater than the other reports. A poor control of glycemic was showed.

According to Onyechi et al.(11), the factors that were significantly more common among type 2 diabetic patients with the presence of microalbuminuria were assessed by multiple logistic regression analysis. The following variables were independently associated with microalbuminuria after adjustment for age and sex: presence of retinopathy(OR=3.04; 95%CI, 1.65 to 5.62, P-value < 0.001), HbA1c(OR= 2.13; 95%CI, 1.20 to 3.78, P-value <0.01), Total cholesterol(OR=1.82, 95%CI, 1.06 to 3.14, P-value<0.05), duration of diabetes(OR=1.65, 95%CI, 1.12 to 2.68, P-value < 0.02), and systolic blood pressure(OR=1.95, 95%CI, 1.56 to 2.37, P-value<0.03).

Hypertension

This present study showed that systolic Blood Pressure was clearly a potential risk factors in the development of microalbuminuria. Association between systolic blood pressure and microalbuminuria was found in the study subjects who had systolic blood pressure more than or equal 130 mmHg were 1.35 times more likely to develop microalbuminuria(OR = 1.35, 95%CI 1.07 to 1.69, P-value = 0.008)(Table 11) compared to those with a systolic blood pressure less than 130 mmHg. But diastolic blood pressure was not significant(OR = 1.02, 95%CI 0.84 to 1.24, P-value = 0.826)(Table 11). After simultaneously adjust for multiple variables by multiple logistic regression analysis, systolic blood pressure was still significant(OR = 1.51,

95%CI 1.13 to 2.16, P-value =0.007)(Table 12). This is in agreement with the study of Gall at al.(63). So, this study suggested that a dose effect between systolic blood pressure and microalbuminuria was found more OR increase the more exposure increase, suggesting a causal association.

As stated in literature, It has been postulated that increased blood pressure, through an effect on blood flow has been hypothesized to damage the renal capillary endothelial cells, resulting in the development and progression of microalbuminuria. The presence of hypertension increases the risk of atherosclerotic vascular disease and microvascular complications(98). Patients with type 2 diabetes are at least twice as likely to have hypertension as the nondiabetic population(99).In Japanese Cohort, The systolic blood pressure and the fasting plasma glucose level were demonstrated as independent risk indicators for microalbuminuria.(92)

Buranakitjaroen P. et al.(50) showed mean blood pressure was 139.13± 15.73 / 81.41± 8.00 mmHg in hypertensive patients with type 2 diabetes and presence microalbuminuria in Thailand. For this study, mean blood pressure was 144.5± 21.3 / 79.4± 11.4 mmHg(Table 10). Both studies were study in Thai people. Almost one-third of Thai patients achieved the target systolic blood pressure less than 130 mmHg, recommended by the American Diabetes Association for adequate blood pressure control at the time of study initiation(100)

HDL

HDL was a strong a risk factors of microalbuminuria in this study. Association between HDL and microalbuminuria was found in the study subjects who had HDL less than 40 mg/dl in male and less than 50 mg/dl in female were 1.48 times more likely to develop microalbuminuria(OR = 1.48, 95%CI 1.12 to 1.95, P-value = 0.004)(Table 11) compared to those with HDL more or equal 40 mg/dl in male and more or equal 50 mg/dl in female. But after adjusting for the effect of other variables, it was still significant(OR = 2.52, 95%CI 1.52 to 4.21, P-value < 0.001)(Table 12).

The result corresponded with the study of Hertzel C. et al.(103), Hashim R et al.(48), Bruno G. et al.(15).

Duration of diabetes

In this study, the relation between duration of diabetes and microalbuminuria was found significant in subjects who had duration of diabetes between 10 – 14.9, 15-19.9 and more or equal 20 years(OR = 1.88, 95%CI 1.41 to 2.51, P-value <0.001; OR = 2.33, 95%CI 1.64 to 3.31, P-value < 0.001; OR = 2.08, 95%CI 1.48 to 2.94, P-value <0.001, respectively) (Table 11) compare to those with duration of diabetes less than 5 years. But after adjusting for the effect of other variables the relation between duration of diabetes and microalbuminuria was found significant in subjects who had duration of diabetes between 5 – 9.9 were 1.59 times(OR = 1.59, 95%CI 1.08 to 2.34, P-value=0.020).And the subjects who had duration of diabetes between 10-14.9, 15-19.9 and more or equal 20 years(OR = 2.38, 95%CI 1.56 to 3.64, P-value <0.001; OR= 3.21 95%CI 1.95 to 5.31, P-value < 0.001; OR = 2.17 95%CI 1.32 to 3.57, P-value =0.002, respectively).

Schmitz et al.(65) assessed the relationship between HbA_{1c} and the progression of albuminuria over four years. However a multiple regression analysis in patients with at least four years and (complete) 6 years of follow-up found that HbA_{1c} was not a significant predictor of rate of increase in albuminuria. Adler AI(101) has shown that the proportion of patients with type 2 diabetes who develops microalbuminuria is substantial namely 25% after 10 years.

BMI

In this study, BMI more than or equal 30 kg/m^2 and 25-29.9 30 kg/m^2 were found to be significant associated with microalbuminuria(OR=1.71, 95%CI 1.24 to 2.37, P-value<0.001, OR=1.46, 95%CI 1.13 to 1.88, P-value=0.003, respectively) (Table 11) but after adjusting for the effect of other variables, it was still significant

only BMI more than or equal 30 kg/m^2 and 25-29.9 30 kg/m^2 (OR=2.09, 95%CI 1.28 to 3.42, P-value=0.003, OR=1.57, 95%CI 1.09 to 2.27, P-value=0.014, respectively)) (Table 12). A relation between body mass index and microalbuminuria has been found in several studies(52, 62, 63), although not universally, whereas Hashim R et al.(48) have not found association. The evidence of an association between basal body mass index and increased albumin excretion is equivocal.

Looker et al.(102) examined weight changes occurring before and after the diagnosis of diabetes and the association of these changes with microvascular complications. They found that before diagnosis of diabetes, the highest body mass index generally occurred at or immediately after diagnosis(0-2 years).

Smoking

In this study found that , cigarette smoking was significantly associated with microalbuminuria. The study subjects who had cigarette smoking were 1.44 times(OR = 1.44, 95%CI 1.13 to 1.85, P-value = 0.003)(Table 11) compare to those with not smoking. After adjusting for effect of other variables, it was significant(OR = 1.42, 95%CI 1.03 to 1.96, P-value =0.034)(Table 12). This result was supported by many previous studies(103)

Smoking accelerates loss of renal function in patients with diabetic and non-diabetic. Patients should be counseled to stop smoking.

CHAPTER VI
CONCLUSION AND RECOMMENDATIONS

Summary of the main finding.

This study was subanalysis of data from Diabetic Registry Project. This project was a cross-sectional clinical based epidemiology study and multicenter study . A study was conducted from period of April to December 2003 at 11 diabetic clinic, Rajavithi Hospital, Chulalongkorn Hospital, Maharat Nakhon Ratchasima Hospital, Theptarin General Hospital, Phramongkutklao Hospital & Medical College, Ramathibodi Hospital, Maharat Nakhon Chiang Mai Hospital, Siriraj Hospital, Prince of Songkhla University,Bangkok Metropolitan medical college and Vajira Hospital and Khon-Kaen University. There were 2 major purpose. First,to study prevalence of microalbuminuria in type 2 diabetes. Second to identify risk factors associated with microalbuminuria in type 2 diabetes.

In 1,734 type 2 diabetes, 926 patients were a microalbuminuria group and 808 patients without microalbuminuria. Majority of subjects were female and old age(50 – 69 years). Most of them from primary school with no occupation.

Prevalence rate of microalbuminuria for Diabetes registry project were 53.4%. The researcher identified 17 articles on microalbuminuria prevalence among the 80 included in Meta Analysis. Pooled prevalence rates show variation across various subgroup categories. Microalbuminuria prevalence were 35.9%(95%CI: 27.9 to 43.9).

The analysis using sequential logistic regression modelling applied to these data yields the following results for 2 model:

1. Reduce Model:

$$\text{logit } P(x) = a + b_1(\text{AGE}) + b_2(\text{SEX})$$

$$\text{logit } P(x) = -0.2329+0.0091(\text{AGE})-0.2848(\text{SEX})$$

2. Full Model:

$$\text{logit } P(x) = a + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 + b_5x_5 + b_6x_6 + b_ix_i$$

logit P(x) = -2.103+0.002(AGE)-0.063(SEX)+0.229(HbA1c)+0.011(SBP)-0.020(HDL_C)+0.034(duration of dm)+ 0.246(smoke)+0.045(BMI).

The variables include in the study were fasting blood sugar, HbA1c, creatinine, total cholesterol, HDL-C, LDL-C, triglyceride, systolic blood pressure, diastolic blood pressure, body mass index, age of onset and duration of diabetes.

In univariated analysis, the factors found to be significantly associated with microalbuminuria were HbA1c, systolic blood pressure, total cholesterol, HDL-C, duration of diabetes, smoking, body mass index.

After adjusting for the possible confounder, 5 factors were significantly associated with microalbuminuria. Systolic blood pressure was found to be significant among who had systolic blood pressure more or equal 130 mmHg(OR=1.51, 95%CI 1.13 to 2.16, P-value = 0.007). HDL-C less than 40 mg/dl in male and less than 50 mg/dl in female were associated with microalbuminuria(OR= 2.52, 95%CI 1.52 to 4.21, P-value<0.001). This study showed that duration of diabetes was associated with microalbuminuria. The odd ratio of duration of diabetes between 5-9.9, 10-14.9, 15-19.9 and more or equal 20 years were 1.59, 95%CI 1.08 to 2.34, 2.38, 95%CI 1.56 to 3.64, 3.21, 1.95 to 5.31 and 2.17, 95%CI 1.32 to 3.57, respectively. Smoking was found to be significant among who ever or current smoking(OR=1.42, 95%CI 1.03 to 1.96, P-value=0.034). There are association between body mass index and microalbuminuria. The odd ratio of body mass index more or equal 30 $kg/m^{2.}$ were 2.09 times(OR=2.09, 95%CI 1.28 to 3.42, P-value=0.003) compare with body mass index between 18.5-22.9 $kg/m^{2.}$

This study showed that systolic blood pressure, HDL-C, duration of diabetes, smoking and body mass index at more or equal 25 kg/m^2 were independent risk factors of microalbuminuria.

The implementation and recommendations.

1. The result from this study suggest the baseline data and factors contributing to microalbuminuria.

2. To reduce the prevalence of microalbuminuria risk factors such as systolic blood pressure, HDL-C, HbA1c and smoking should be seriously managed.

3. Screening and intervention programmes should be implemented as early as possible. Annual screening for microalbuminuria is recommended by the American Diabetes Association(104), the use of semi-quantitative dipstrick test is easy, and provides immediate and accurate results(105). Then should be annual screening for microalbuminuria is recommended for all patients with type 2 diabetes.

Recommendations for future research.

1. The relationship between microalbuminuria and diabetic complication in type 2 diabetes: Cohort study.

2. The results in this study represent only diabetic patient at tertitary hospital. The result should confirm with data of microalbuminuria in other hospitals in different level of hospital.

3. Survival rates in Thai type 2 diabetes who had microalbuminuria.

4. Economic evaluation of the microalbuminuria screening in type 2 diabetic population.

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APPENDIX

Eligibility, quality and data extraction forms

Eligibility criteria:

Study ID Number

	Initials of reviewer	
A1. Does this study include subjects with diabetes mellitus?	☐ NO	☐ YES
A2. Is this a cross sectional study?	☐ NO	☐ YES
A3. Has urinary albumin been measured?	☐ NO	☐ YES
A4. Does this study publication between January 1980 - June 2006?	☐ NO	☐ YES

Decision to Exclude

If the answer to A1. or A2 or A3 or A4 is NO then exclude.

Overall decision

☐ Exclude ☐ Include

Quality criteria:

Study ID Number

	Initials of reviewer	
B1. Was the normalalbuminuric group selected from the same population as the microalbuminuric ?	☐ NO	☐ YES
B2. Does this study include subjects with only type 2 diabetic?	☐ NO	☐ YES
B3. Does this article report the prevalence rate of microalbuminuria in type 2 diabetes?	☐ NO	☐ YES
B4. Does this article report the number of patient with and without microalbuminuria?	☐ NO	☐ YES

Decision to Exclude

If the answer to B1. or B2 or B3 or B4 is NO then exclude.

Overall decision

☐ Exclude ☐ Include

Data Extraction:

C1. Study ID Number

C2. Initials of reviewer

C3. Title

C4. Author and date of publication:

C5. Country and City where study carried out:

C6. In which language is this article?

C7. How many subjects are there in the study?

C8. Which analytical method was used for measurement of urinary albumin?

C9. Which statistical methods were used in this study?

C10. How is microalbuminuria defined in this study?

C11. Was this study carried out in type 2 diabetes subjects? ☐ NO ☐ YES

C12. Was this study carried out in type 2 diabetes subjects? ☐ NO ☐ YES

C13. Was this study based on population based? ☐ NO ☐ YES

C14. Was this study based on Hospital based? ☐ NO ☐ YES

C15. Was this study carried out Multi –center ? ☐ NO ☐ YES

Meta Analysis

Assessment of homogeneity among results

Test of Homogeneity

$$H_o : P_1 = P_2 = P_k = P$$

$$H_A : P_1 \neq P_2 \neq P_k \neq P$$

The pooled prevalence was calculated as

$$\overline{P} = \frac{\sum w_i \hat{p}_i}{\sum w_i}$$

where $\overline{P}$ was the pooled prevalence of the microalbuminuria in type 2 diabetes,

p_i was the prevalence of microalbuminuria in the ith study and

w_i was 1/var(p_i), which was weight of each study.

$$w_i = \frac{1}{\hat{p}_i(1-\hat{p}_i)/n_i}$$

A random effects model assumes that each observed prevalence rate differs from the population mean by subject –level sampling error plus a value that represents other sources of variability associated assumed to be randomly distribution.(106)

A fixed effects model assumes that prevalence rate heterogeneity(between study differences) is due to unobserved random sources, may believe that it has systematic sources and can be explained by the independent variables in the meta-analysis

Heterogeneity of prevalence across studies was checked as follows:

$$Q = \sum w_i (\hat{p}_i - \overline{p})^2$$

The Q statistic follows a chi-square distribution with number of studies (k)-1 df. If heterogeneity was present, between study variation was then estimated as follows:

$$\tau^2 = \frac{Q-(k-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \quad \text{if } Q > \text{k-1 or } 0 \text{ otherwise.}$$

This was used to calculate a weight term that accounted for between study variation:

$$w_i^* = \frac{1}{\text{var}(\hat{p}_i) + \tau^2},$$

and the pooled prevalence was estimated as follows:

$$\overline{P}^* = \frac{\sum w_i^* \hat{p}_i}{\sum w_i^*}$$

The 95 percent confident interval was estimated as follows:

$$95\%CI = \overline{p^*} \pm \frac{1.96}{\sqrt{\sum w_i^*}}$$

studyID	population	n	study design	pi	1-pi	wi	wi^2	wi * pi	P_bar	pi-pbar	(pi-pbar)^2
Varghese(2000)	South india	1425	cross-sectional	0.363	0.637	6162.669	37978483.04	2237.049		0.036	0.0013
TKW Tam(2003)	Hong Kong	1161	cross-sectional	0.134	0.866	10004.83	100096538.4	1340.647		-0.193	0.0371
Ahmedani MY(2005)	Pakistan	2100	Multi-center	0.34	0.66	9358.289	87577568.7	3181.818		0.013	0.0002
Lee KU(1995)	Koreans	631	cross-sectional	0.2	0.8	3943.75	15553164.06	788.75		-0.127	0.0160
Hashim(2004)	Lahore	150	cross-sectional	0.467	0.533	602.625	363156.9324	281.4259		0.140	0.0197
Bruno G(1996)	Italy	1967	Population-base	0.321	0.679	9024.633	81444002.11	2896.907		-0.006	0.0000
Erasmus(1992)	Nigreria	113	cross-sectional	0.565	0.435	459.7701	211388.5586	259.7701		0.238	0.0568
Leza-Torres O(2005)	Coahuila	301	cross-sectional	0.853	0.147	2400.491	5762358.305	2047.619		0.526	0.2771
Annemilke(2006)	Amsterdam	195	cross-sectional	0.172	0.828	1369.228	1874785.8	235.5072		-0.155	0.0239
Mattock(1992)	English	141	cross-sectional	0.25	0.75	752	565504	188		-0.077	0.0059
Dasmahapatra(1994)	African-American	116	cross-sectional	0.31	0.69	542.3095	294099.5834	168.1159		-0.017	0.0003
Alzaid(1994)	Saudi Arabian	184	cross-sectional	0.413	0.587	758.9788	576048.8848	313.4583		0.086	0.0075
Klein(1984)	American	798	Population-base	0.26	0.74	4147.609	17202661.64	1078.378		-0.067	0.0044
Masoud R.M(2004)	USA	590	cross-sectional	0.259	0.741	3074.214	9450789.262	796.2213		-0.068	0.0046
Onyechi(2000)	Bahraini	312	cross-sectional	0.25	0.75	1664.00	2768896.00	416.00		-0.077	0.0059
Peera(2005)	Thai(DM&HT)	97	cross-sectional	0.433	0.567	395.0943	156099.5166	171.0758		0.106	0.0113
DRP(2003)	Thai	1742	Multi-center	0.534	0.466	7000.37	49005176.07	3738.197		0.207	0.0430
		12023			sum	61660.86	410880720.9	20138.94	0.326608		

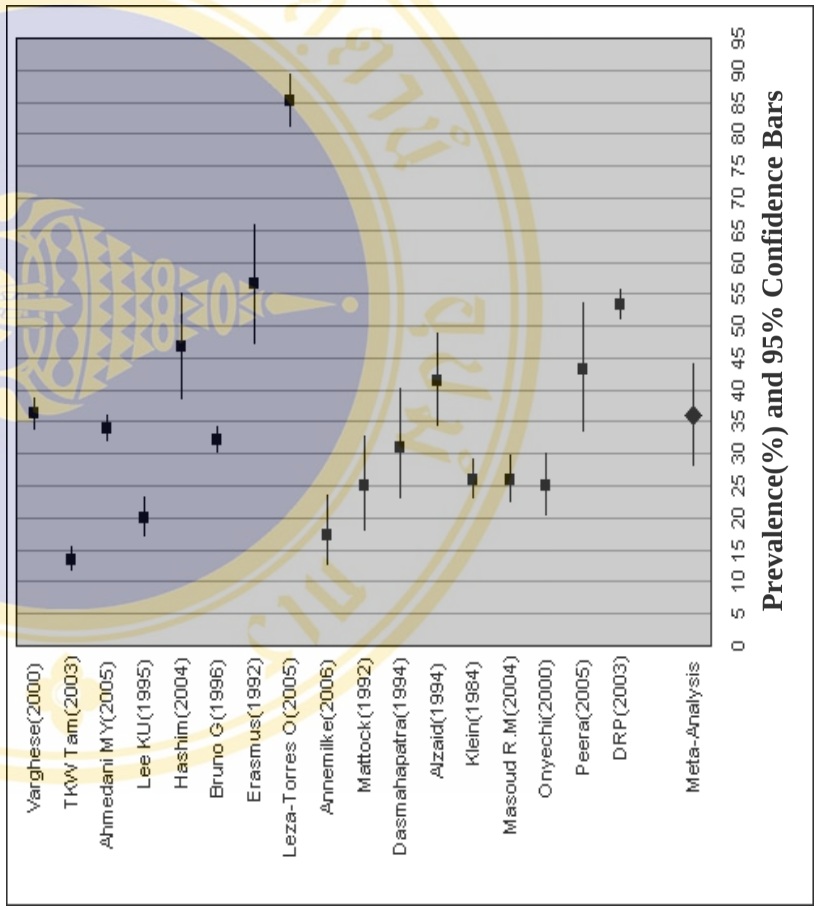
studyID	population	⋯	wi*((pi-pbar)^2)	vi	wi*	wi*_pi
Varghese(2000)	South india	⋯	8.162	0.000162	35.915	13.037
TKW Tam(2003)	Hong Kong	⋯	371.158	0.000100	35.995	4.823
Ahmedani MY(2005)	Pakistan	⋯	1.678	0.000107	35.987	12.235
Lee KU(1995)	Koreans	⋯	63.217	0.000254	35.798	7.160
Hashim(2004)	Lahore	⋯	11.878	0.001659	34.082	15.916
Bruno G(1996)	Italy	⋯	0.284	0.000111	35.981	11.550
Erasmus(1992)	Nigreria	⋯	26.129	0.002175	33.494	18.924
Leza-Torres O(2005)	Coahuila	⋯	665.148	0.000417	35.590	30.358
Annemilke(2006)	Amsterdam	⋯	32.730	0.000730	35.197	6.054
Mattock(1992)	English	⋯	4.413	0.001330	34.470	8.617
Dasmahapatra(1994)	African-American	⋯	0.150	0.001844	33.869	10.499
Alzaid(1994)	Saudi Arabian	⋯	5.665	0.001318	34.484	14.242
Klein(1984)	American	⋯	18.401	0.000241	35.814	9.312
Masoud R.M(2004)	USA	⋯	14.052	0.000325	35.706	9.248
Onyechi(2000)	Bahraini	⋯	9.766	0.000601	35.358	8.839
Peera(2005)	Thai(DM&HT)	⋯	4.472	0.002531	33.099	14.332
DRP(2003)	Thai	⋯	301.095	0.000143	35.940	19.192
				sum	596.778	214.339

Q =	1538.397
Q-(k-1) =	1522.397
(sum wi -(sum wi^2/sum wi) =	54997.297
P value =	*0.0277*
Prevalence	0.359
sqrt sum wi*	24.429
95%CI(Upper)	0.439
95%CI(lower)	0.279

Meta Analysis

Study	Population	Number	study design	Prevalence	95%CI	
				Rate	Lower	Upper
Varghese(2000)	South india	1,425	cross-sectional	36.3	33.8	38.8
TKW Tam(2003)	Hong Kong	1,161	cross-sectional	13.4	11.5	15.5
Ahmedani MY(2005)	Pakistan	2,100	Multi-center	34.0	31.9	36.1
Lee KU(1995)	Koreans	631	cross-sectional	20.0	16.9	23.3
Hashim(2004)	Lahore	150	cross-sectional	46.7	38.5	55.0
Bruno G(1996)	Italy	1,967	Population-base	32.1	30.0	34.2
Erasmus(1992)	Nigreria	113	cross-sectional	56.5	47.0	65.9
Leza-Torres O(2005)	Coahuila	301	cross-sectional	85.3	80.9	89.2
Annemilke(2006)	Amsterdam	195	cross-sectional	17.2	12.4	23.5
Mattock(1992)	English	141	cross-sectional	25.0	17.9	32.8
Dasmahapatra(1994)	African-American	116	cross-sectional	31.0	22.8	40.3
Alzaid(1994)	Saudi Arabian	184	cross-sectional	41.3	34.1	48.8
Klein(1984)	American	798	Population-base	26.0	22.9	29.1
Masoud R.M(2004)	USA	590	cross-sectional	25.9	22.4	29.7
Onyechi(2000)	Bahraini	312	cross-sectional	25.0	20.3	30.2
Peera(2005)	Thai(DM&HT)	97	cross-sectional	43.3	33.3	53.7
DRP(2003)	Thai	1,742	Multi-center	53.4	51.0	55.8
Meta-Analysis	**17**	**12,023**		**35.9**	**27.9**	**43.9**

Forest Plots



Sample size calculation was based on the logistic regression model:

Result of fitting a logistic regression model to the southern India data. (Varghese et al.) n= 1,425

Variable	b	S_b	p-value	Odds ratio(95%CI)
Age	0.25	0.06	<0.0001	1.3(1.1 to 1.4)
DBP	0.43	0.08	<0.0001	1.5(1.3 to 1.8)
HbA1c	0.29	0.068	<0.0001	1.3(1.2 to 1.5)
FBS	0.23	0.074	0.002	1.3(1.1 to 1.5)
Duration of DM	0.18	0.052	0.005	1.2(1.1 to 1.3)

Regression Coefficient

The estimated value of Beta (regression coefficient), denoted b_i . These are calculated using the Newton-Raphson method to solve the nonlinear, maximum likelihood equations.

Standard Error

The standard error of bi. This is an estimate of the precision of the Beta estimate. The covariance matrix is obtained by inverting the observed information matrix evaluated at the maximum likelihood estimates. The standard errors are the square roots of the diagonal elements of this covariance matrix.

Chi-Square Beta = 0

The one degree of freedom Chi-square statistic for testing the hypothesis that = 0 against the alternative 0. This is calculated as follows:

$$\chi_i^2 = \left(\frac{bi}{s_{bi}} \right)^2$$

Prob Level

The probability of obtaining a Chi-square value greater than the above. This is the significance level of the test. If this value is less than some predefined alpha level, say 0.1, then the variable is said to be statistically significant.

R-Squared

The amount that this variable adds to the overall R-squared when it is added to the logistic regression equation. This is an approximate R-squared value. Some authors have advised against its use completely because it does not behave like its counterpart in multiple regression. We suggest a great deal of caution be exercised when using this value. It is calculated as follows:

Parameters needed for the calculation of the sample size, values used and source of information.

$$\text{Then} \quad R^2 = \frac{\chi_i^2}{\chi_i^2 + n - p - 1}$$

$$= 0.0199$$

Parameter	Description	Value	source
P_0	Estimated prevalence of microalbuminuria among type 2 diabetes patient	0.36	A. Varghese et al.
R^2	Multiple correlation coefficient of the covariate DBP with the remaining covariates(e.g. HbA1c)	0.0199	calculation
$Z_{1-\alpha}$	Percentile at(1-α)% of standard normal curve in two tailed test with α = 0.05	1.645	Determination
Z_{β}	Percentile at(1-β)% of standard normal curve with β = 0.2	0.842	Determination

$$n = \frac{1 + 2P_0\delta}{1 - R^2} \times \frac{(Z_{1-\alpha} + Z_{1-\theta}e^{-0.25\beta_i^{*2}})^2}{P_0\beta_i^{*2}}$$

Where $\beta_i^{*2} = [\ln(1.5)]^2 = 0.16$

$$\delta = \frac{1+(1+\beta_1^{*2})e^{1.25\beta_i^{*2}}}{1+e^{-0.25\beta_i^{*2}}}$$

$$= 1.24$$

$$n = \frac{(1+2*0.36*1.24)}{1-0.0199} \times \frac{(1.645+0.842\times e^{-0.25(0.16)})^2}{0.36\times 0.16}$$

$$= 197$$

Diabetes Registry 2003
Data Collection Form

Patient's Initial ☐☐☐ **ID** ☐☐☐ site ☐☐☐☐☐ running number

วันที่เก็บข้อมูล ☐☐ dd ☐☐ mm **พ.ศ. 25** ☐☐ yy **เลขที่บัตรประชาชน** ☐☐☐☐☐☐☐☐☐☐☐☐☐

ชื่อ _____ **สกุล** _____ **HN** ☐☐☐☐☐☐☐☐☐☐

DEMOGRAPHY

เพศ ☐ ชาย ☐ หญิง

วันเกิด ☐☐ dd ☐☐ mm **พ.ศ.** ☐☐☐☐ yyyy

อาชีพ ☐ ว่างงาน ☐ ใช้แรงงาน ☐ แม่-พ่อบ้าน ☐ ใช้ฝีมือ ☐ วิชาชีพ ☐ นักเรียน-นักศึกษา

การศึกษา ☐ ไม่ได้เรียน ☐ ประถมศึกษา ☐ มัธยมศึกษา ☐ ปวช./ปวส. ☐ ปริญญาตรี ☐ ปริญญาโท ☐ ปริญญาเอก

สิทธิค่ารักษาพยาบาล ☐ จ่ายเงินเอง ☐ เบิกราชการ/รัฐวิสาหกิจ ☐ ประกันสังคม ☐ โครงการ 30 บาท ☐ ประกันสุขภาพเอกชน ☐ บัตรสงเคราะห์

ที่อยู่ที่สามารถติดต่อได้

บ้านเลขที่ _____ หมู่ _____ ตำบล _____ อำเภอ _____ จังหวัด _____ รหัสไปรษณีย์ ☐☐☐☐☐

โทรศัพท์ที่บ้าน (___) _____ โทรศัพท์ที่ทำงาน (___) _____ ต่อ _____ มือถือ (___) _____

MEDICAL HISTORY

Date of diagnosis ☐☐ dd ☐☐ mm **พ.ศ.** ☐☐☐☐ yyyy

Diagnosis ☐ Type 1 DM ☐ Type 2 DM ☐ Uncertain ☐ Other (Please specify) _____

MONITORING DATA (RISK & COMPLICATIONS)

Height ☐☐☐ cm

Weight ☐☐☐.☐ kg

BP ครั้งแรก (พักก่อนวัด BP ครั้งแรก 5 นาที และวัดในท่านั่งแขนขวา) ☐☐☐ / ☐☐☐ mmHg

BP ครั้งที่สอง (วัดห่างจาก BP ครั้งแรก 30 นาที) ☐☐☐ / ☐☐☐ mmHg

Smoking ☐ No ☐ Yes ☐ Ex-smoker _____ yr **Alcohol** ☐ No ☐ Yes ☐ Abstinence _____ yr

Blood Chemistry

Latest FBS* ☐☐☐ mg/dl	**T Chol** ☐☐☐ mg/dl	**TG** ☐☐☐☐ mg/dl
Latest HbA1C* ☐☐.☐ %	**HDL-C** ☐☐☐ mg/dl	
Cr ☐☐.☐ mg/dl	**LDL-C** ☐☐☐ mg/dl	

Complication

	No	Yes	N/A	If yes, complete below
Nephropathy	☐	☐	☐	☐ UMA ☐ Proteinuria ☐ RI (Cr ≥ 2) : result from ▽ spot morning urine ▽ 24 hrs urine protein ▽ strip
Renal replacement therapy	☐	☐		☐ Hemodialysis ☐ Peritoneal dialysis ☐ Kidney transplantation
Retinopathy	☐	☐	☐	☐ NPDR ☐ PDR ▽ Laser RX ▽ No Laser RX
Cataract	☐	☐	☐	
Legal blindness	☐	☐	☐	Cause: ☐ DM ☐ non DM
Hx of foot ulcer	☐	☐		
Amputation	☐	☐		☐ AK ☐ BK ☐ Toes
Absence of peripheral pulse	☐	☐		
Vascular by pass graft	☐	☐		
Hx of IHD	☐	☐	☐	☐ Possible ☐ Definite
Revascularization	☐	☐		☐ CABG ☐ PTCA
Hx of CVA	☐	☐		☐ Ischemia ☐ Hemorrhage ☐ Unknown
Hx of hypertension	☐	☐		
Hx of dyslipidemia	☐	☐		

MEDICATIONS

Insulin	☐ Yes	☐ No	**TZD**	☐ Yes	☐ No	**β-blocker**	☐ Yes	☐ No	**Statin**	☐ Yes	☐ No
Sulfonylurea	☐ Yes	☐ No	**α-GI**	☐ Yes	☐ No	**α-blocker**	☐ Yes	☐ No	**Fibrate**	☐ Yes	☐ No
Glinide	☐ Yes	☐ No	**ACE-I**	☐ Yes	☐ No	**CCB**	☐ Yes	☐ No	**ASA**	☐ Yes	☐ No
Metformin	☐ Yes	☐ No	**ARB**	☐ Yes	☐ No	**Diuretic**	☐ Yes	☐ No	**Herbal**	☐ Yes ☐ เคย	☐ No

FAMILY HISTORY OF DM

Family history ☐ No ☐ Yes; If Yes specify ☐ Father ☐ Mother ☐ Sister (same F&M) ☐ Brother (same F&M)

IF THE PATIENT IS 14 YEARS OLD OR LESS

Age of puberty: Male: Pubarche _____ **Female: Menarche** _____

Investigator's signature _____ Date _____

BIOGRAPHY

NAME Miss Sirima Mongkolsomlit

PLACE OF BIRTH Bangkok, Thailand

INSTITUTIONS ATTENDED Kuakarun college of nursing, 1993 :
Bachelor of Nursing.
Mahidol University, 1998 :
Graduate Diploma(Health information system).
Mahidol University, 2006 :
Master of Science(Public Health).
Major in Infectious disease and Epidemiology.

POSITION&OFFICE Clinical Research Collaboration Network, Bangkok, Thailand
Position : Research Coordinator
Tel 08 7018 9103
E-mail mongkolsomlit@yahoo.com

HOME ADDRESS 200/1 moo 13 minburi
Bangkok, Thailand
Tel 0 2517 1318