RISK OF CORONARY HEART DISEASE IN TYPE 2 DIABETES MELLITUS PATIENTS IN KELANTAN

by

NURUL AKMAR BINTI GHANI

Dissertation submitted in partial fulfillment of the requirements for the Degree of Master of Science (MEDICAL STATISTICS)

UNIVERSITI SAINS MALAYSIA

2011

ACKNOWLEDGEMENTS

Alhamdulillah, praise to Allah S.W.T., the most compassionate and most merciful, for always being there for me all the time, giving me blessing and strength to complete this dissertation. Special thanks dedicated to my beloved parents, Ghani Mahamud, Fatimah Musa, and my family for the unconditional love and support they give me all the time. Million thanks and appreciations go to the following people, who helped me a lot in preparing this dissertation;

- My supervisor, Dr. Aniza Abdul Aziz, for her support, encouragement, advices, comments, suggestions, contributions and patience throughout the research and completion of this dissertation
- My co-supervisor, Prof Madya Dr Norsa'adah Bachok, for her help, comments, patience and support throughout the completion of this dissertation
- My course coordinator, Prof. Dr. Syed Hatim Noor @ Nyi Nyi Naing, for his help, comments and suggestions with the statistical analysis part of this dissertation
- The "National Economic Burden and Cost Effectiveness of Type 2 Diabetes Mellitus Outpatient Care" researcher, Dr Wan Norlida Ibrahim, for her help, assistance and support in the data collection for this study
- My colleagues and Universiti Sains Malaysia for the guidance and support
- Ministry of Health, Malaysia for their permission to use the data in the study.
- And everyone who involved in this study directly or indirectly

Thank you...

TABLE OF CONTENT

ACKNOWLEDGEMENTS.....ii

TABLE OF CONTENT.....iii

LIST OF TABLES.....vii

LIST OF FIGURES.....ix

LIST OF ABBREVIATIONS.....xi

LIST OF APPENDICES.....xii

ABSTRAK.....xv

ABSTRACT.....xvii

CHAPTER ONE: INTRODUCTION.....1

CHAPTER TWO: LITERATURE REVIEW.....6

2.1 The definition of Type 2 Diabetes Mellitus.....6

2.2 Pathogenesis of Type 2 Diabetes Mellitus.....7

2.3 Diagnosis of Diabetes Mellitus and Current Criteria.....8

2.4 Management of T2DM.....9

2.5 Complications of T2DM.....10

2.6 Morbidity of cardiovascular and coronary heart disease in diabetes.....11

2.7 Mortality of cardiovascular and coronary heart disease in diabetes.....12

2.8 Risk factors of developing CHD among T2DM patients.....13

2.8.1 Age.....13

2.8.2 Gender.....13

2.8.3 Race.....14

2.8.4 Glycaemic control.....14

2.8.5 Comorbidities.....15

2.8.6 Microalbuminuria.....16

2.8.7 Socioeconomic factors.....16

2.8.8 Other biochemicals.....17

2.10 Conceptual Framework.....19

CHAPTER THREE: OBJECTIVES.....21

3.1 General objectives.....21

3.2 Specific objectives.....21

3.3 Research questions.....22

3.4 Research hypotheses.....22

3.5 Operational definitions.....23

CHAPTER FOUR: METHODOLOGY.....24

4.1 Study design.....24

4.2 Study location.....24

4.3 Study duration.....25

4.4 Reference population.....25

4.5 Source population.....25

4.6 Sampling frame.....25

4.7 Inclusion and exclusion criteria.....26

4.8 Sampling method.....26

4.9 Sample size calculation.....27

4.10 Mode of data collection.....29

4.11 Definition of study outcomes.....29

4.12 Definition of independent variable.....30

4.13 Flow chart.....31

4.14 Statistical analysis.....34

4.14.1 Data exploration and cleaning.....34

4.14.2 Descriptive statistic.....34

4.14.3 Univariable analysis.....35

4.14.4 Multivariable analysis.....35

4.14.5 Ethical approval.....37

CHAPTER FIVE: RESULTS.....38

5.1 Profile of T2DM Patients.....38

5.1.1 Sociodemographic characteristic.....38

5.1.2 Clinical characteristics.....40

5.2 Survival probabilities of developing CHD in T2DM patients.....42

5.2.1 Overall probabilities.....42

5.2.2 Ten year survival probabilities of developing CHD according to sociodemographic subgroups.....43

5.2.3 Ten year survival probabilities of developing CHD according to clinical characteristics.....49

5.2.4 Comparison of survival probabilitites in sociodemographic and clinical subgroups.....56

5.3 Risk factors of developing CHD among T2DM patients.....59

5.3.1 Simple Cox Regression.....59

5.3.2 Preliminary main effect model (PMEM).....62

5.3.2a Interaction and multicollinearity.....63

5.3.2b Checking proportional hazards assumptions.....63

5.3.2c (a) Martingale residuals.....68

5.3.2c (b) Cox Snell residuals.....69

5.3.2c (c) Deviance residuals.....70

5.3.2c (d) Influential diagnostic assessment.....71

5.4 Final Model.....73

CHAPTER SIX: DISCUSSION.....74

6.1 Overall survival probabilitites of developing CHD in T2DM patients.....74

6.2 Survival probabilities according to sociodemographic and clinical characteristic.....76

6.3 Risk factors of developing CHD in T2DM patients in Kelantan.....79

6.4 Limitations of the study.....84

CHAPTER SEVEN: CONCLUSION.....86

CHAPTER EIGHT: RECOMMENDATION.....87

REFERENCES.....88

APPENDICES.....89

LIST OF TABLES

Table	*Title*	*Page*
Table 2.1	Diagnostic values for Diabetes Mellitus Type 2/Glucose on Tolerance – oral glucose tolerance test (OGTT)	9
Table 2.2	Targets for Type 2 Diabetes Mellitus	10
Table 4.1	Sample size calculation	28
Table 5.1(a)	Sociodemographic characteristics of T2DM patients in Kelantan	39
Table 5.1(b)	Clinical characteristics of T2DM patients in Kelantan	41
Table 5.2	Survival probabilities of developing CHD in T2DM patients in Kelantan	43
Table 5.3(a)	Ten year survival probabilities of T2DM patients developing CHD in Kelantan according to sociodemographic characteristics	57
Table 5.3(b)	Ten year survival probabilities of T2DM patients developing CHD in Kelantan according to clinical characteristics	58
Table 5.4(a)	Risk factors of developing CHD among T2DM patients in Kelantan using Simple Cox Regression for sociodemographic subgroups	60
Table 5.4(b)	Risk factors of developing CHD among T2DM patients in Kelantan using Simple Cox Regression for clinical characteristics	61

Table 5.5	Risk factors of developing CHD among T2DM patients in Kelantan using Multivariable Cox Proportional Hazard Regression in PMEM	62
Table 5.6	Test of proportional hazard assumption	66
Table 5.7	The risk factors associated with T2DM patients developing CHD in Kelantan using Multivariable Cox Proportional Hazard Regression	73
Table 6.1	Survival studies on developing of CHD in T2DM patients	76
Table 6.2	Risk factors of developing CHD in T2DM patients identified in other studies	83

LIST OF FIGURES

Figure	*Title*	*Page*
Figure 2.1	Conceptual Framework	20
Figure 4.1	Overview of time to event outcome of this study	30
Figure 4.2	Flow chart of study 1	32
Figure 4.3	Flow chart of study 2	33
Figure 5.1	Overall Kaplan Meier survival curve for survival probabilities of developing CHD in T2DM patients in Kelantan	42
Figure 5.2(a)	Kaplan Meier survival curves for age group	44
Figure 5.2(b)	Kaplan Meier survival curves for gender	45
Figure 5.2(c)	Kaplan Meier survival curves for ethnicity	45
Figure 5.2(d)	Kaplan Meier survival curves for education level	46
Figure 5.2(e)	Kaplan Meier survival curves for marital status	46
Figure 5.2(f)	Kaplan Meier survival curves for occupation	47
Figure 5.2(g)	Kaplan Meier survival curves for salary group	47
Figure 5.2(h)	Kaplan Meier survival curves for household income group	48
Figure 5.2(i)	Kaplan Meier survival curves for variable duration of diagnosis	57
Figure 5.2(j)	Kaplan Meier survival curves for frequency of follow up	51
Figure 5.2(k)	Kaplan Meier survival curves for compliance to follow up	51
Figure 5.2(l)	Kaplan Meier survival curves for insulin	52
Figure 5.2(m)	Kaplan Meier survival curves for diabetic control status	52
Figure 5.2(n)	Kaplan Meier survival curves for hypertension	53

Figure 5.2(o)	Kaplan Meier survival curves for dyslipidemia	53
Figure 5.2(p)	Kaplan Meier survival curves for retinopathy	54
Figure 5.2(q)	Kaplan Meier survival curves for nephropathy	54
Figure 5.2(r)	Kaplan Meier survival curves for neuropathy	55
Figure 5.2(s)	Kaplan Meier survival curves for stroke	55
Figure 5.3(a)	Hazard function plot for stroke	64
Figure 5.3(b)	Hazard function plot for hypertension	64
Figure 5.4(a)	Log minus log plot for variable stroke	65
Figure 5.4(b)	Log minus log plot for variable hypertension	65
Figure 5.5(a)	Scaled Schoenfeld residual plot for variable stroke	67
Figure 5.5(b)	Scaled Schoenfeld residual plot for variable hypertension	67
Figure 5.6	Martingale residual plot	68
Figure 5.7	Cox Snell residual plot	69
Figure 5.8	Deviance residual plot	70
Figure 5.9(a)	Df-beta residual plot for variable stroke	72
Figure 5.9(b)	Df-beta residual plot for variable hypertension	72

LIST OF APPENDIXES

Appendix	*Title*
Appendix A	Consent form
Appendix B	Research data collection form
Appendix C	Universiti Sains Malaysia ethical approval letter
Appendix D	National Medical Research and Registry approval letter

LIST OF ABBREVIATIONS

α	Significance level
A	accrual time
ADA	American Diabetes Association
Apo	Apolipoprotein
bFGF	Basic Fibroblast Growth Factor
CHD	Coronary heart disease
CI	Confidence Interval
CPG	Clinical Practice Guideline
CVD	Cardiovascular disease
df	degree of freedom
DCDCP	Diabetes Care Data Collection Project
DM	Diabetes mellitus
ECG	Electrocardiograph
F	Additional follow up time after end of recruitment
FG	Fasting glucose
FH	Familial hypercholesterolemia
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HF	Health facilities
HR	Hazard Ratio
HUSM	Hospital Universiti Sains Malaysia
IF	Inflammation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance

IHD	Ischemic heart disease
IR	Insulin resistance
LDL	Low density lipoprotein
LML	Log minus log
LR	Likelihood ratio
m	ratio of control to experimental patients
m1	median survival time on control to treatment
MI	Myocardial infarction
MTHFR	Methylenetetrahydrofolate reductase
n	Sample size
NB	Nisbah Bahaya
NHMS	National Health and Morbidity Survey
NMRR	National Medical Research Registry
OGTT	Oral glucose tolerance test
OR	Odd Ratio
PH	Proportional hazard
PS	Power and sample calculation
QALY	Quality adjusted life years
R	Hazard ratio of control treatment relative to experimental obtained from literature
SD	Standard deviation
SK	Selang Keyakinan
SPSS	Statistical Package for Social Science
STATA	Statistics/Data Analysis
t	time
T2DM	Type 2 Diabetes Mellitus

TNF-α	Tumor necrosis factor-α
TSA	Total sialic acid
TVC	Time-varying covariate
UKPDS	United Kingdom Prospective Diabetes Study
USM	Universiti Sains Malaysia
VIF	Variation Inflation Factor
WHO	World Health Organization
$1-\beta$	Power

ABSTRAK

Pengenalan: Penyakit kencing manis jenis 2 adalah masalah utama di seluruh dunia dan penyakit ini menyebabkan pelbagai jenis komplikasi, termasuk penyakit jantung koronari. Kajian ini dijangka dapat membantu pengurusan pesakit kencing manis jenis 2, agar risiko untuk mendapat penyakit jantung koronari dan komplikasi-komplikasi lain kencing manis dapat dikurangkan.

Objektif: Untuk menentukan kebarangkalian mandiri dan faktor-faktor risiko untuk mendapat penyakit jantung koronari dalam kalangan pesakit kencing manis jenis 2 di Kelantan.

Metodologi: Seramai 249 pesakit kencing manis jenis 2 yang hadir di klinik kencing manis di Kelantan dan memenuhi kriteria telah dianalisis. Reka bentuk kajian yang adalah tinjauan rekod retrospektif, Status penyakit jantung koronari ditentukan melalui dokumentasi diagnosa oleh doktor dan bacaan elektrokardiograf (ECG). Analisis Kaplan Meier *Product Limit*, ujian ringkas dan berganda regresi Cox Proportional Hazard telah digunakan untuk mengenal pasti kebarangkalian mandiri dan faktor-faktor yang berkaitan.

Keputusan: Kebarangkalian mandiri secara keseluruhan untuk mendapat penyakit jantung koronari dalam kalangan pesakit kencing manis di Kelantan adalah 79.2% (95% Selang Keyakinan (SK): 69.0%, 86.4%). Kadar 10 tahun kemandirian adalah 82.2% (SK: 84.0%, 92.8%). Perbezaan kemandirian yang bererti secara statistik melalui ujian Log

Rank adalah pesakit yang mempunyai penyakit angin ahmar dan darah tinggi. Faktor-faktor prognostik yang dikenal pasti dalam kajian ini adalah angin ahmar [Nisbah Bahaya (NB) terselaras: 3.72 (95% SK: 1.41, 9.77), P=0.008] dan darah tinggi [NB terselaras: 3.84 (95% SK: 0.91, 16.15), P=0.066].

Kesimpulan: Kemandirian dan faktor risiko untuk mendapat penyakit jantung koronari dalam kalangan pesakit kencing manis jenis 2 yang diperolehi adalah sama dengan kajian lain. Kajian ini menunjukkan bahawa pesakit kencing manis jenis 2 yang mempunyai angin ahmar dan darah tinggi lebih berisiko untuk mendapat penyakit jantung koronari di Kelantan.

ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) has become a major health problem worldwide and this disease leads to a wide range of complications, including coronary heart disease (CHD). The research findings obtained are expected to help in management of T2DM patients, in order to decrease the risk of developing CHD, as well as other diabetic complications.

Objectives: To determine the survival probabilities and identify the risk factors of developing CHD among T2DM patients in Kelantan

Methods: A total of 249 T2DM patients attending diabetic clinics in Kelantan who fulfilled the inclusion criteria were included in the analysis. The study design was retrospective record review. The patients' CHD status were determined based on documented diagnosis by medical officer and electrocardiograph (ECG) reading. Kaplan Meier Product Limit Estimates, Simple and Multiple Cox regressions were performed to determine the statistically significant risk factors of developing CHD among T2DM patients in Kelantan.

Results: Overall survival probabilities of developing CHD in T2DM patients in Kelantan was 79.2% (95% CI: 69.0%, 86.4%). The 10 year survival probabilities of developing CHD in T2DM patients was 82.2 (95% CI: 84.0%, 92.8%). Significant differences of survival probabilities of developing CHD using Log Rank test were found in hypertension and stroke. The significant prognostic factors found in this study were

stroke [Adjusted HR: 3.72 (95% CI: 1.41, 9.77), P=0.008] and hypertension [Adjusted HR: 3.84 (95% CI: 0.91, 16.15), P=0.066].

Conclusions: Overall survival rate of developing CHD in T2DM patients obtained in this study was approximately equivalent to other studies. The findings revealed that stroke and hypertension were the prognostic factors of developing CHD among T2DM patients in Kelantan.

CHAPTER 1

INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (T2DM) is a major worldwide health problem that causes mortality and morbidity. It is characterized by hyperglycemia and listed as one of the chronic diseases in human. Diabetes is known to increase the risk of developing many types of diseases (Fowler, 2008). The incidence of diabetes mellitus (DM) is growing rapidly, and so its complications. Developing countries recorded higher increase of diabetic patients' numbers than other countries (WHO, 2006).

Globally, the number of diabetic patients in 2005 was estimated to be approximately 171 million. It was expected to be 300 million by 2025 (WHO, 2006). Eight percent of the adult population is affected by diabetes mellitus which is approximately 170 million people worldwide and the estimated number of diabetes mellitus patients is expected to increase by 50 to 70 percent in the next 25 years (Coccheri, 2007).

T2DM problem is a growing concern in America because of rising prevalence of obesity (Wilson, 2001). Eight percent of type 2 diabetic patients in the United States is obese or overweight (Berry *et al.*, 2007). It was estimated that 15.7 million Americans

have T2DM which accounted about 5.9 percent of the whole population, where only two-third of them were detected and treated actively (Ramlo-Halsted & Edelman, 2000). In Asia, mortality rate caused by diabetes mellitus was increasing by two-folds over the past ten years in Taiwan (Chen & Li, 2007). More women in Latin America and Middle East have diabetes and diabetes prevalence is significantly increasing among people aged more than 65 years old (Wild *et al.*, 2004).

According to the first National Health and Morbidity Survey (NHMS I) conducted in 1986, the prevalence for diabetes mellitus was 6.3 percent, and rose to 8.2 percent in 1996 when the NHMS II was conducted. The prevalence increased to 14.9 percent when NHMS III was carried out in 2006. World Health Organization (WHO) predicted that the total number of diabetics in Malaysia will be 2.48 million in 2030, a 164 percent increase compared to the number in 2000 which was 0.94 million (Mafauzy, 2006). The prevalence of diabetes in Malaysia increases with age where 8.3 percent of population aged over 30 years has diabetes. People aged 60 to 64 years old have the highest prevalence of known and undiagnosed diabetes. Moreover, females were more at risk to get diabetes than men in Malaysia (Zaini, 2000). The prevalence for diabetes mellitus in Kelantan was reported to be above 10.5 percent. Furthermore, 38.4 percent of diabetics in Kelantan was obese or overweight, higher than those with normal glucose tolerance. The prevalence of diabetics among people with normal glucose tolerance accounted for only 24.1 percent (Mafauzy, 2006).

Chronic diabetes complications present at some point of diagnosis. Diabetes complications vary from acute manifestation such as coronary artery disease and stroke to severe systemic infections. Diabetes treatment attempts to lower the chance of tissue bodies harmed by hyperglycemia. Harmful effects of hyperglycemia are divided into macrovascular complications such as coronary artery disease, peripheral arterial disease and stroke, and microvascular complications such as diabetic nephropathy, neuropathy and retinopathy (Fowler, 2008). The Diabetes Care Data Collection Project (DCDCP) was conducted in 1993 in Malaysia, aimed to determine the prevalence of diabetes mellitus and impaired glucose tolerance among different ethnic groups in Malaysia. In that study which involved 6836 patients, it was estimated that 58 percent had neuropathy, 53 percent had retinopathy, 0.8 percent was legally blind, 0.9 percent required dialysis, 8.6 percent had cardiovascular disease (CVD), 5.6 percent had stroke and 1.9 percent had leg amputation (Ali *et al.* as cited by Zaini, 2000).

Macrovascular disease has been the major cause of death among diabetic patients. A study done by Fowler (2008) showed that the relationship between diabetes and macrovascular disease such as coronary heart disease (CHD) and stroke was highly correlated. CHD is highly prevalent in diabetic patients. Chanudet *et al.* (2007) reported that the risk of developing CHD in diabetics was two to three-folds higher than non diabetics. Thus, undergoing a healthier lifestyle is very important to those with diabetic and pre-diabetic in order to avoid risky complications later.

In the United States, approximately $132 billion spent annually on the prevention policy for diabetes that affects about 18 million people (Apostolos *et al.*, 2009). It was estimated that the cost per quality-adjusted-life-years (QALY) of beginning the intensive lifestyle intervention for impaired glucose tolerance (IGT) for intervention compared to no intervention was $62,600 and $35,400 respectively (Vlajinac *et al.*, 1992). After the onset of diabetes, the cost per QALY for an intensive lifestyle intervention was $24,500 (Engelgau, 2005). These findings proved that diabetes mellitus also affects patients financially as the cost of the treatment is high and costly. When patients are hospitalized due to diabetes or its complications, the cost is inflated. Unfortunately, increasing incidence of diabetes in developing countries will worsen the burden of cost in these parts of the world (Ibrahim *et al.*, 2010).

1.2 Rationale of the study

Most of the observational studies that reported the risk factors of CHD development were conducted in developed countries (Bertoni *et al.*, 2004; Turner *et al.*, 1998 & Tuttolomondo *et al.*, 2008). There are very minimal published research data on risk of developing CHD among T2DM patients in local setting (Rahman *et al.*, 2006). In addition, the risk estimates produced are highly influenced by the differences of demography, culture and belief (Zaini, 2000). Risk factors identified through this study could provide information in planning and making decision in CHD prevention in our community. In turn, this would improve survival rate of CHD among T2DM patients.

Several studies have been done to find the association between T2DM and CHD (Tuttolomondo *et al.*, 2008 & Xiang *et al.*, 2004). Majority of them used logistic regression to estimate the risk. There was only small number of studies conducted to find the hazard ratio of CHD among T2DM patients (Bertoni *et al.*, 2004; Turner *et al.*, 1998 & Yang *et al.*, 2008). This study aims to investigate and estimate the hazard ratio of developing CHD among diabetic patients, taking all possible variables that may affect the risk of complication. The hazard ratio is used to predict time to develop CHD once T2DM is diagnosed in a patient. Measurement of survival probabilities and hazard ratio for T2DM patients developing CHD provides alternative analysis on estimation of the risk of developing CHD among T2DM patients according to time.

Previous studies reported a few consistent risk factors of developing CHD in diabetes such as hypertension, hypercholesterolemia and obesity (Bertoni *et al.*, 2004; Xiang *et al.*, 2004 & Yang *et al.*, 2008). Nevertheless, only a few studies that looked into the influence of socioeconomic in development of CHD in DM. This study was carried out to investigate also the role of socioeconomic status as risk factors of CHD in diabetes.

Cohort study design which was widely applied in previous study demands time and high resources. This study used retrospective cohort design which allows rapid and feasible method in assessing hazard of CHD in diabetics. Unless Malaysia conducts specific diabetes cohort study, this study has its own value in contributing important information on our patients' risk.

CHAPTER 2

LITERATURE REVIEW

2.1 The definition of Type 2 Diabetes Mellitus

'Diabetes' word comes from Ionian Greek which means 'to pass through'. The term diabetes mellitus was started to be used around eighteenth century by John Rollo and others to differentiate the honeyed taste of urine from other normal and tasteless polyuric states (Alexander *et al.,* 2000). Claude Bernard has contributed a lot in the understanding of diabetes in nineteenth century, as he discovered a lot about the disease. He illustrated glycogen, the glucose storage in the liver and acute hyperglycemia which leads to medulla oblongata damage, which is known as 'piqure' diabetes. Langerhans suggested that production of glucose lowering substance is done by pancreatic islets, which was then named insulin by Jean de Meyer in 1909 (Ekoe *et al.*, 2001). Even though diabetes has been known since centuries ago, there was no clearly accepted definition of it until early 80s. WHO Expert Committee on diabetes mellitus in 1980 defined it as a chronic hyperglycemia state that resulted from the combination of genetic and environment factors (WHO, 2006)

There are two types of diabetes mellitus, type 1 diabetes mellitus and type 2 diabetes mellitus. Type 1 diabetes occurs when both genetic and environmental factors act

together in the pancreatic beta cells that lead to the onset of diabetes (Ekoe *et al.*, 2001). The diabetes with insulin resistance and without severe insulin deficiency or beta cells dramatic loss is known as T2DM. It is also called as non insulin dependent diabetes due to an early asymptomatic stage with insulin resistance to mild postprandial hyperglycemia to frank diabetes (Johnstone & Veves, 2005). As a heterogeneous disorder, there are three basic metabolic defects that characterize the disease, which are, the resistance of insulin, non autoimmune-mediated insulin secretory defect and glucose production increased by the liver (Ramlo-Halsted and Edelman, 2000).

2.2 Pathogenesis of Type 2 Diabetes Mellitus

The metabolic defects that cause diabetes mellitus are the resistance of insulin, β-cell dysfunctions and damaged hepatic glucose production triads. The disposition of insulin resistance can be recognized by a subnormal response to certain amount of insulin concentration. It can be measured circuitously by the level of fasting insulin level, the higher the insulin level, the higher is the degree of insulin resistance (Ramlo-Halsted and Edelman, 2000). The decline of insulin levels causes the decrease in insulin's inhibitory effects, leading to the higher hepatic glucose production. As hepatic glucose production increases, the glucagon production is also increased, thus glucose production will also rise. This metabolic sequences cause hyperglycemia for years or even decades before proceeded to type 2 diabetes (Ekoe *et al.*, 2001).

2.3 Diagnosis of Diabetes Mellitus and current criteria

Diabetic symptoms include thirst, polyuria, polydypsia, blurring of vision, weight loss and infections which are not severe and may be absent in some patients (Ekoe *et al.*, 2001). The criteria for diagnosis of diabetes mellitus that was introduced by American Diabetes Association (ADA) in 1997 was fasting glucose (FG) more than 7.0 mmol/L or 126 mg/dl and impaired FG between 6.0 to 6.9 mmol/L or 110 to 125 mg/dl (Alexander *et al.*, 2000).

According to Malaysian Clinical Practice Guideline (CPG) 2009, the confirmation for the diagnosis is done by the measurement of venous plasma glucose. One abnormal glucose value is done to test the symptomatic individual, but for asymptomatic individual, two abnormal glucose values are required. Patients are confirmed as diabetes if they have fasting venous plasma glucose and random venous plasma glucose of $\geq$7 mmol/L and $\geq$11.1mmol/L, respectively. The test using oral glucose tolerance test (OGTT) values are illustrated in Table 2.1.

Table 2.1: Diagnostic values for Diabetes Mellitus Type 2/Glucose on Tolerance – oral glucose tolerance test (OGTT)

OGTT Plasma Glucose Values (mmol/L)		
Category	**0-hour**	**2-hour**
Normal	< 6.1	<7.8
IFG	6.1 – 6.9	-
IGT	-	7.8 – 11.0
DM	≥ 7.0	≥ 11.1

IFG Impaired fasting glucose **IGT** Impaired Glucose Tolerance **DM** Diabetes Mellitus

(Ministry of Health Malaysia, 2009)

2.4 Management of T2DM

After being diagnosed as diabetic, symptomatic patients should be treated promptly. Main aims of T2DM management are to improve quality of life and avoid premature death. The short term objective for this management is to relieve the symptoms and acute complications. Appropriate glycemia achievement, concurrent risk factors reduction and chronic complications identification and treatment are added for long term objectives. The target for diabetic control is shown in Table 2.2 (Ministry of Health Malaysia, 2009).

Table 2.2: Targets for Type 2 Diabetes Mellitus

Parameter	**Levels**
Glycaemic Control	
Fasting	4.4 – 6.1 mmol/L
Non-fasting	4.4 – 8.0 mmol/L
HbA1c	< 6.5%
Lipids	
Triglycerides	≤ 1.7 mmol/L
High density lipoprotein (HDL) cholesterol	≥ 1.1 mmol/L
Low density lipoprotein (LDL) cholesterol	≤ 2.6 mmol/L
Exercise	150 mins/week
Blood pressure	
Normal renal function	≤ 130/80 mmHg
Renal impairment/Gross Proteinuria	≤ 125/75 mmHg

(Ministry of Health Malaysia, 2009)

2.5 Complications of T2DM

Diabetes complications can be divided into two main categories, macrovascular and microvascular complications. Macrovascular complications are coronary heart disease, cerebrovascular disease, diabetic foot and erectile dysfunction. Diseases under microvascular complication are retinopathy, nephropathy and neuropathy.

Patients should be screened for possible complications that may affect them. Those who should be screened for CHD are patients with peripheral or cerebrovascular disease, patients who lead sedentary lifestyle, age more than 35 years old and patients who smoke, have high cholesterol level, high blood pressure, have family history of CHD and have positive microalbuminuria or macroalbuminuria test. CHD is assessed by performing a resting electrocardiograph (ECG) and application of established cardiovascular risk assessment tools (Ministry of Health Malaysia, 2009).

2.6 Morbidity of cardiovascular and coronary heart disease in diabetics

Patients with chronic hyperglycemia have a greater risk for cardiovascular disease (CVD) (Brinke *et al.*, 2008). Diabetic patients have a higher risk of coronary artery disease and revascularization procedure than non diabetic subjects, by which the relative hazard is between one and three (Chen & Li, 2007). Type 2 diabetes caused two times increased risk of coronary heart disease compared to non diabetes. It has been reported that diabetic patients are more susceptible to CVD disorders such as myocardial infarction (MI) (Smith *et al.,* 1999). Forty nine percent of diabetic offsprings had coronary atherosclerosis, and they were at risk for myocardial infarction, ventricular dilation, high-grade atherosclerosis and multivessel disease. Moreover, diabetic subjects showed worse prognosis of clinical CHD than non diabetic subjects (Alexander et al., 2000). Ledru *et al.* (2001) evaluated the severity of coronary disease among diabetic and non diabetic subjects and found that it was more severe in diabetic than in non diabetic.

About 25 percent of those undergoing revascularization was diabetic patients, and the outcomes after revascularization were usually worse than non-diabetic patients (Berry *et al.*, 2007). Diabetic subjects had more extensive coronary calcifications, higher prevalence of left main stem disease and reduced coronary collateral artery recruitment (Berry *et al.*, 2007). In patients with diabetes mellitus, apart from coronary atherosclerosis, cardiac disturbances are also caused by other factors such as cardiac microangiopathy, neuropathy and myocardial subcellular organelles changes (Takeda, 2010).

2.7 Mortality of cardiovascular and coronary heart disease in diabetics

Over one-half of deaths among DM patients in the United States were represented by CVD (Berry *et al.*, 2007). In Taiwan, about 19.8 percent death of diabetic patients is caused by CVD (Chen & Li, 2007). Mortality due to CVD in T2DM patients was 3 times higher compared to general population worldwide. Death due to cerebrovascular and CHD is higher by two to four time among diabetic patients, compared to non-diabetic ones (Abdella *et al.*, 2000). Both diabetes and MI were associated with CHD mortality and a longer duration of diabetes contributed to a stronger predictor of mortality among men with diabetes (Cho *et al.*, 2002).

2.8 Risk factors of developing coronary heart disease (CHD) among Type 2 diabetes mellitus patients

2.8.1 Age

Diabetes and older age act together in increasing the frequency and severity of CHD, with the more severe diabetic patients to have higher mortality factor and serious clinical consequences (Chanudet *et al.,* 2007). Among diabetics, people aged more than 84 years old have an average hazard ratio (HR) of 18.1 (95% CI: 12.7, 25.7) for MI and 16.7 (95% CI: 14.6, 19.0) for ischemic heart disease. Coronary revascularization procedures increased with age up to 74 years old, with HR of 11.1 (95% CI: 8.7, 14.1) for diabetic group (Chen & Li, 2007).

2.8.2 Gender

Typically, T2DM caused CHD risk to be doubled in men and tripled in women (Wilson, 2001). A meta-analysis showed that diabetes was a stronger risk factor in women than men, which was about 50 percent higher, meanwhile the prevalence for ischemic heart disease was higher among diabetic women than non diabetic men in every age group (Wirehn *et al.,* 2007). Significant interaction between age and gender in diabetes was found and overall HR of CHD with respect to diabetes was approximately two (Chen & Li, 2007). Higher relative hazards in diabetic patients was found in both sexes and among diabetic patients, higher HR was observed in female, for all kind of CHD. The HR for coronary revascularization was higher in males than

females in both diabetic and control group (Chen & Li, 2007). However, the magnitude of differences between genders varies across studies (Wirehn *et al.*, 2007).

2.8.3 Race

South Asians had higher mortality from CHD compared to other populations, and this was believed to be caused by metabolic disturbance which was also related to insulin resistance. McKeigue and colleagues (2000) had performed a study that compared South Asians settled in United Kingdom with the European group, and found that the prevalence of diabetes mellitus, high blood pressure, high fast and post-glucose serum insulin concentration, high plasma triglyceride and low high density lipoprotein cholesterol concentration were higher in those South Asians compared to Europeans group. Between 1979 and 1983 in England and Wales, CHD mortality for age standardized was 40 percent higher in men and women from South Asians compared to other population (Das, 1995). In Japan, patients of T2DM were usually non obese, thus the mortality incidence due to CHD was lower compared to patients of DM in European and North America. However, data of white population cannot be used in Asian population due to the differences in demography and culture (Asakawa *et al.*, 2000).

2.8.4 Glycaemic control

Many studies agree that decreasing percentage of hemoglobin A1c (HbA1c) leads to decrease risk of developing CHD. The relationship between CVD and HbA1c level is

clear. A meta-analysis study reported an increase of 1 percent in HbA1c results in increase of CVD risk by 1.2 percent (Ray *et al.*, 2009). Stratton et al. (2000) showed that with an HbA1c of more than 10 percent, the risk of developing CHD was up to 34 percent, while with an HbA1c of less than 6 percent, the risk was reduced up to 17 percent. The best reduction could be achieved when HbA1c was as low as 7 percent (Brinke, 2008). In the intensive treatment over 5 years that requires patients to take medication such as sulphonylurea, insulin, metformin, acarbose and gliclazide, reduction of the concentration of HbA1c by 0.9 percent resulted in a significant 17 percent reduction of non-fatal myocardial infarction, 15 percent reduction of coronary heart disease and non significant 7 percent reduction for stroke (Ray *et al.*, 2009). Decreasing percentage of HbA1c caused CHD and mortality risks to be lower (Berry *et al.*, 2007).

2.8.5 Co morbidities

The three well-known risk factors that are believed to be associated with CHD and death in diabetic patients were elevated blood cholesterol levels, hypertension and cigarette smoking (Anjana *et al.*, 2008). CHD prevalence in diabetics was higher in hypertensive subjects (Vlajinac *et al.*, 1992). In the investigation of Multiple Risk Factor Intervention Trial, the CVD death risk in diabetes increased by twofold and more after other risk such as smoking habit, hypertension and elevated cholesterol were included (Wilson, 2001).

2.8.6 Microalbuminuria

Microalbuminuria without specific intervention not only progresses to overt nephropathy and end-stage renal failure, but also leads to cardiovascular complications and death. Microalbuminuria is an important marker for macrovascular damage and cardiovascular events. It confirms the presence of common ground such as microangiopathy and macroangiopathy (Mattock *et al.,* 1998). Enhanced pituitary-adrenal activity was associated with cardiovascular complications, while cortisol secretion was associated and correlated with macrovascular and microvascular complications in diabetic patients (Coccheri, 2007).

2.8.7 Socioeconomic factors

In Malaysia, urban areas had significantly higher prevalence of diabetes, compared to rural areas, 6.8 percent versus 4.5 percent, respectively (Letchuman *et al.,* 2010). DCDCP study in 1993 found that level of diabetes control was highly related with socioeconomic factors, occupation and educational status. Differences in background influenced change in dietary habits, knowledge and environment, NHMS Study in 1996 showed that Felda settlers seemed to be a significant predictor to glucose intolerance, thus, nutritionists together with dieticians and clinicians were spearheaded to the intervention program at their community (Zaini, 2000).

Urbanisation does affect physical activity and body-mass index. In Asian countries that experience rapid socioeconomic progress such as India and China, diabetes prevalence

is higher due to lifestyle and diet change. Urban lifestyles influence unhealthy diet which include higher intake of refined carbohydrate, processed food, saturated, total fat and low fibre intake. Nutrition transition is so huge that it causes chronic diseases, not only diabetes, but also stroke, hypertension and many more (Ramachandran *et al.*, 2010)

2.8.8 Other biochemicals

Apolipoprotein (Apo) e4 allele presence in T2DM was reported to be associated with the increased risk of coronary artery disease and impairment of endothelium-dependant dilation. A study concluded that the risk of CAD death in elderly diabetic patients was increased by the presence of Apo e4 allele (Xiang *et al.*, 2004). Neopterin, a strong predictor of fatal ischaemic heart disease (IHD) in diabetic patients, might be the plaque-specific marker for both atherosclerosis and diabetes (Vengen *et al.*, 2008).

Increased baseline plasma bFGF had been thought to be associated with the occurrence of CHD in adults who had T2DM for a long time. CHD patients had a higher increase of basic fibroblast growth factor (bFGF) compared to the baseline level during the five to seven years study treatment, even though substantial improvements had been done in most CVD risk factors (Zimering *et al.*, 2010). Leptin and insulin also affected the CHD risk through insulin resistance manipulation (Ruige *et al.*, 2005). Tumor necrosis factor-α (TNF-α) was also thought to be related with cardiovascular process, by which it played role in the pathophysiology pathway, specifically through lipid metabolism, obesity susceptibility and insulin resistance modulation. High level of TNF-α mRNA

was found in vascular cells in a human atherosclerosis lesions study, which showed that the direct regulation of the mRNA transcription rate was higher when the LDL particles was exposed to macrophages. High level of TNF secretion was also being observed in hypercholesterol rabbits and low density lipoprotein (LDL) receptor knockout mice (Vendrell *et al.*, 2003).

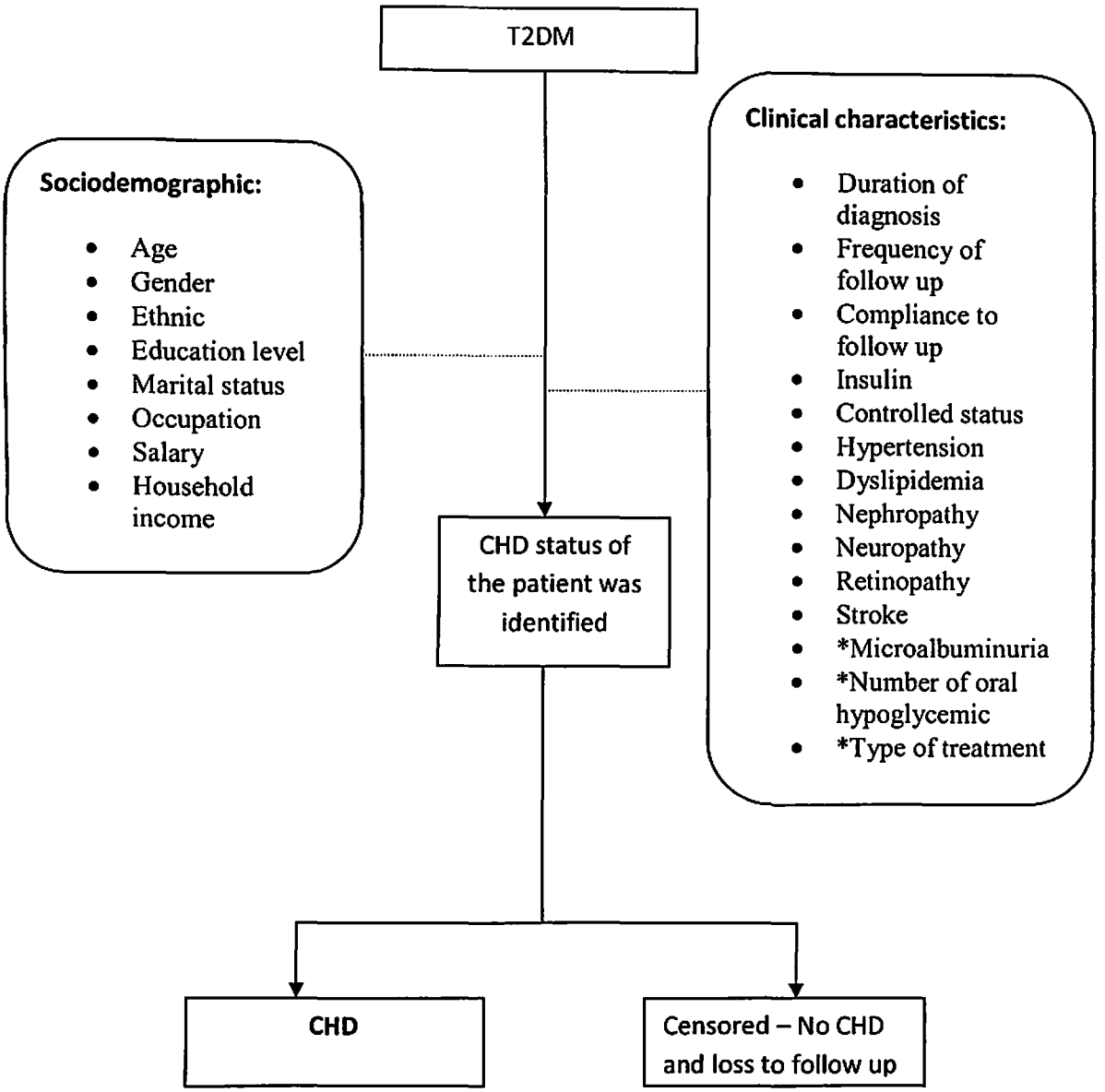
Studies done demonstrated that plasma levels of thrombin-antithrombin III complex and fibrinogen were elevated among diabetic patients (Takahashi *et al.* (1989), Ganda and Arkin (1992) and Ceriello (1997) as cited by Asakawa *et al.*, 2000). Elevated levels of serum total sialic acid (TSA), an acute phase response marker had been reported among Caucasian population with CVD, especially T2DM subjects. The observed TSA mean concentration was reported to be the same as the mean reported in Malays and India in Malaysia (Abdella *et al.*, 1999).

Dyslipidaemia is another risk factor for CHD among diabetic patients which leads to recommendation that LDL cholesterol reduction should be looked into more seriously in treating diabetic dyslipidaemia (Tuomilehto, 2003). Apart from diabetes duration and glycaemic control, atherosclerosis in T2DM is also influenced by dyslipidaemia, insulin resistance, hypertension and genetic factors. These are the factors that could accelerate diabetes-induced atherosclerosis. Methylenetetrahydrofolate reductase (MTHFR) enzyme which is important in homocysteine metabolism is also believed to relate with CHD. Its mutation might be a risk factor for CHD. MTHFR genotype and allele frequencies between T2DM patient with and without CHD are significantly different (Sun *et al.*, 2005).

Yanagi *et al.* (1997) reported about a genetic disorder called familial hypercholesterolemia (FH), which was characterized by high levels of serum low dentisty lipoprotein (LDL) cholesterol and premature coronary atherosclerosis influence glucose metabolism of CAD to be abnormal. FH patients with impaired glucose metabolism should be given special attention and treatment to avoid the advancement of coronary atherosclerosis. Study by Anjana *et al.* (2008) illustrated that the risk of glucose intolerance, together with cardiometabolic risk factors such as obesity, low HDL cholesterol and hypertension increase in patients with parental history of T2DM.

2.9 Conceptual Framework

Figure 2.1 shows the conceptual framework of this study. Patients diagnosed as T2DM who attended primary and tertiary diabetic clinics in Kelantan were followed to observe their CHD status and possible risk factors of developing CHD. Two major characteristics that had been investigated in this study are sociodemographic and clinical characteristics.



*Not included in the study

Figure 2.1: Conceptual Framework

CHAPTER 3

OBJECTIVE

3.1 General objective

To evaluate the survival probabilities of coronary heart disease and its risk factors in T2DM patients in Kelantan

3.2 Specific objectives

1. To determine the survival probabilities of CHD in T2DM patients in Kelantan
2. To compare the differences of survival probabilities of CHD in T2DM patients by socio-demographic and clinical characteristics subgroups in Kelantan
3. To identify the risk factors of CHD among T2DM patients in Kelantan

3.3 Research Question

1. What are the overall survival probabilities of CHD in T2DM patients in Kelantan?
2. What are the survival probabilities of CHD in T2DM patients by socio-demographic and clinical characteristics subgroups in Kelantan?
3. What are the risk factors of CHD among T2DM patients in Kelantan?

3.4 Research Hypotheses

1. The survival probabilities of CHD in T2DM patients are different according to socio-demographic and clinical characteristics.
2. Age, gender, ethnic, marital status, occupation, education level, household income, diabetes controlled status, duration of diabetes, insulin, frequency of follow up, compliance to follow up, hypertension, dyslipidemia, nephropathy, neuropathy, retinopathy and stroke are the risk factors of CHD among T2DM in Kelantan.

3.5 Operational definitions

Type 2 diabetes mellitus patients in this study is defined as patients who are documented as T2DM by the attending medical officer, who have undergone measurement of venous plasma glucose and diagnosed as T2DM by their respective plasma glucose measurements.

Patients that fulfill the criteria listed below based on documentation in the medical records are considered as **coronary heart disease** in this study:

i) Diagnosed as having CHD or IHD by the attending medical officer/physician

ii) ECG changes suggestive of myocardial ischaemia

- ST elevation, ST depression and Q wave with documented complain of chest pain to indicate acute ischaemia
- T inversion with documented medical officer/physician decision to treat as CHD or IHD

Hazard ratio is defined as a risk measure of developing CHD in T2DM.

Risk factors in this study refer to variables that are associated with the risk of developing CHD in T2DM patients.

Survival probabilities is defined as the probabilities of not developing CHD in T2DM patients over time.

CHAPTER 4

METHODOLOGY

4.1 Study Design

The design for this study was a retrospective record review. Data from the patients' medical record were reviewed and the related information on variables of interest, patients' diabetic and coronary heart disease status was extracted.

4.2 Study Location

The study was conducted at randomly selected six government diabetic clinics in Kelantan. The diabetic clinics were Kota Bharu Health Clinic, Selising Health Clinic, Batu Gajah Health Clinic, Pasir Mas Health Clinic, Ketereh Health Clinic and Hospital Universiti Sains Malaysia Diabetic Clinic. Only primary health clinics with family medicine specialist were included due to appropriateness of their record keeping.