

**FACTORS AFFECTING DIABETES CONTROL
AND DYSLIPIDAEMIA AMONG TYPE 2
DIABETES MELLITUS PATIENTS IN HOSPITAL
UNIVERSITI SAINS MALAYSIA**

DR. EID MOHAMMAD s/o AKHTAR MOHAMMAD

UNIVERSITI SAINS MALAYSIA

2003

**FACTORS AFFECTING DIABETES CONTROL AND
DYSLIPIDAEMIA AMONG TYPE 2 DIABETES MELLITUS
PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA**

by

**DR. EID MOHAMMAD s/o AKHTAR MOHAMMAD
(MD Kabul University, Afghanistan)**

**Thesis submitted in fulfilment of the
requirements for the degree
of Master of Science**

January 2003

ACKNOWLEDGEMENT

I would like to express my gratitude to all those who have contributed to this work. First, I should grant my deepest appreciation and sincere thanks to my main supervisor, **PROFESSOR DR. MAFAUZY MOHAMED** for his supervision and support throughout my study.

My sincere and special thanks to my co-supervisor, **ASSOCIATE PROFESSOR DR. FARIDAH ABDUL RASHID** for her great help, continuous assistance, invaluable encouragement, guidance, and comments in the writing of this thesis.

My respects and thanks are due to all the staff at the Diabetes Outpatient Clinic and at Clinical Trial Unit especially **SISTER RUBIAH OTHMAN** and **EN. MANAF YUSOF** for their friendly cooperation. Thanks are also due to the head and staff of Chemical Pathology Department (Routine Lab) and Endocrine Lab, HUSM. I would like to extend my thanks to **MR. ZULKIFLI BIN ISMAIL** for his excellent technical assistance. My deepest appreciation to **DR. THAN WINN** for his great help with statistical analysis. Thanks are also due to library staff and workers at the postgraduate computer lab who made all facilities available for my use.

Nevertheless, gratitude is also due to the **Islamic Development Bank** for sponsoring my study.

*DEDICATED TO MY PARENTS,
BELOVED WIFE, AND MY CHILDREN
AYSHA & ABDUL-WASI.*

دغه ڪتاب زما مور او بلار ، شخي
او اولادونو عايشه او عبدالواسع
ته اهداء كوم .

TABLE OF CONTENT

	<u>Page</u>
ACKNOWLEDGEMENT	ii
TABLE OF CONTENT	iii
LIST OF TABLES	x
LIST OF FIGURES	xv
LIST OF ABBREVIATIONS	xxi
ABSTRACT	xxvi
ABSTRAK	xxviii
CHAPTER 1 INTRODUCTION	1
1.1 Prevalence of type 2 diabetes	2
1.2 Diagnosis of diabetes mellitus	6
1.3 Classification of diabetes mellitus	9
1.4 Hyperglycemia	12
1.4.1 Fasting plasma glucose (FPG)	12
1.4.2 Glycated hemoglobin (A1C)	13
1.5 Diabetic dyslipidaemia	15
1.6 Hypertension	27

1.7	Treatment for diabetes mellitus	29
1.7.1	Treatment for controlling of blood glucose	29
1.7.1.1	Clinical targets for glycaemic control in people with diabetes	30
1.7.2	Management of diabetic dyslipidaemia	31
1.7.2.1	Goals of therapy for lipid profile in diabetic patients	32
1.7.2.2	Nonpharmacological strategies	33
1.7.2.3	Antidiabetic agents and modification of lipoprotein levels	34
1.7.2.4	Lipid-lowering drug therapy	35
1.7.2.5	Lipid lowering drugs	39
1.8	Aim of the study	41
1.9	Objectives	42
CHAPTER 2 METHODOLOGY		43
2.1	Ethical approval	44
2.2	Study design	44
2.3	Selection of patients	44
2.4	Inclusion and exclusion criteria	46
2.5	Definition of clinical conditions and terms	46
2.6	Physical examination	50
2.6.1	Height and body weight measurements	50
2.6.2	Blood pressure measurement	50
2.7	Collection of blood sample	51

2.8	Biochemical analysis	52
2.8.1	Determination of glucose	52
2.8.2	Determination of glycated hemoglobin	53
2.8.3	Determination of total cholesterol	54
2.8.4	Determination of HDL cholesterol	55
2.8.5	Calculation of VLDL cholesterol	55
2.8.6	Calculation of LDL cholesterol	56
2.8.7	Determination of triglycerides	57
2.9	Statistical analysis	58
2.9.1	Calculation of sample size	58
2.9.2	Analysis of data	61
CHAPTER 3 RESULTS		62
3.1	Clinical targets for the control of diabetes mellitus in type 2 diabetic patients attending Diabetes Clinic in HUSM	63
3.1.1	Characteristics of type 2 diabetic patients	63
3.1.2	Clinical targets for glycaemic control in type 2 diabetes	80
3.1.2.1	Gender and glycaemic control	80
3.1.2.2	Ethnicity and glycaemic control	82
3.1.2.3	Age and glycaemic control	83
3.1.2.4	Duration of diabetes and glycaemic control	85
3.1.2.5	Family history of diabetes and glycaemic control	86
3.1.2.6	Smoking and glycaemic control	87
3.1.2.7	BMI and glycaemic control	88

3.1.2.8	Multiple Logistic Regression Analysis (A1C)	91
3.1.3	Clinical targets for BMI (obesity) in type 2 diabetes	92
3.1.3.1	Gender and BMI	92
3.1.3.2	Ethnicity and BMI	94
3.1.3.3	Age and BMI	95
3.1.3.4	Duration of diabetes and BMI	98
3.1.3.5	Family history of diabetes and BMI	99
3.1.3.6	Smoking and BMI	100
3.1.3.7	Multiple Logistic Regression Analyses	101
3.1.4	Clinical targets for blood pressure in type 2 diabetes	102
3.1.4.1	Antihypertensive treatment and control of blood pressure	103
3.1.4.2	Gender and control of blood pressure	105
3.1.4.3	Ethnicity and control of blood pressure	107
3.1.4.4	Age and control of blood pressure	109
3.1.4.5	Duration of diabetes and control of blood pressure	111
3.1.4.6	Family history of diabetes and control of blood pressure	113
3.1.4.7	Smoking and control of blood pressure	115
3.1.4.8	BMI and control of blood pressure	117
3.1.4.9	A1C and control of blood pressure	119
3.1.4.10	Multiple Logistic Regression Analyses	121
3.1.5	Clinical targets for lipids in type 2 diabetes	122
3.1.5.1	Lipid-lowering drug therapy	122

3.1.5.2	Proportion of patients with none, one, two, three, or four lipid values outside of the clinical target	126
3.1.5.3	Proportion of male and female patients with one, two, three, or four lipid values outside of clinical target	128
3.1.5.4	Proportion of patients with one, two, three, or four lipid values outside of clinical target in three glycaemic control groups by A1C	130
3.1.5.5	Multiple Logistic Regression Analyses	132
3.2	Pattern of diabetic dyslipidaemia according to American Diabetes Association (ADA) classification of lipoprotein into CVD risk categories	134
3.3	Lipid profile of type 2 diabetic patients who are not on anti-lipid therapy	139
3.3.1	Characteristics of type 2 diabetic subjects who are not on anti-lipid therapy	139
3.3.2	Classification of total, HDL, LDL cholesterol and triglycerides according to NCEP, ATP III	149
3.3.3	Distribution of lipid profile in men and women	155
3.3.4	Ethnicity and lipid profile	159
3.3.5	Age and lipid profile	161
3.3.6	Duration of diabetes and lipid profile	165
3.3.7	Family history of diabetes mellitus and lipid profile	170
3.3.8	Smoking and lipid profile	171
3.3.9	BMI and lipid profile	172
3.3.10	Fasting plasma glucose and lipid profile	181

3.3.11	Glycated hemoglobin and lipid profile	186
3.4	Effect of glycaemic control on lipid profile in type 2 diabetic patients	190
3.4.1	Difference in mean lipid profiles of type 2 diabetic patients according to different levels of fasting plasma glucose	190
3.4.1.1	Difference in mean lipid profiles at fasting plasma glucose of 7 mmol/L	190
3.4.1.2	Difference in mean lipid profiles at fasting plasma glucose of 8 mmol/L	192
3.4.1.3	Difference in mean lipid profiles at fasting plasma glucose of 9 mmol/L	193
3.4.1.4	Difference in mean lipid profiles at fasting plasma glucose of 10 mmol/L	195
3.4.2	Difference in mean lipid profiles of type 2 diabetics patients according to different levels of A1C	199
3.4.2.1	Difference in mean lipid profiles at A1C of 7 %	200
3.4.2.2	Difference in mean lipid profiles at A1C of 8 %	201
3.4.2.3	Difference in mean lipid profiles at A1C of 9 %	204
3.4.2.4	Difference in mean lipid profiles at A1C of 10 %	208
3.4.2.5	Difference in mean lipid profiles in three glycaemic control groups by A1C	212

CHAPTER 4	DISCUSSION	219
4.1	Glycaemic control (A1C)	220
4.2	Body Mass Index (BMI)	221
4.3	Blood pressure	222
4.4	Lipid profile	224
4.4.1	Prevalence of dyslipidaemia	224
4.4.2	Pattern of dyslipidaemia in type 2 diabetic patients	224
4.4.3	Pattern of dyslipidaemia in type 2 diabetic patients who are not on any anti-lipid therapy	226
4.4.4	Contributing factors	227
4.5	Limitations of current study	229
CHAPTER 5	SUMMARY AND CONCLUSION	230
5.1	Summary and conclusion	231
5.2	Recommendations for future research	233
REFERENCES		234
APPENDICES		248
Appendix 1	OFFER LETTER	249
Appendix 2	CONSENT FORM	250
Appendix 3	DATA COLLECTION FORM	251
Appendix 4	LIST OF PUBLICATIONS	252

LIST OF TABLES

		<u>Page</u>
Table 1.1	Criteria for testing for diabetes in asymptomatic adults	4
Table 1.2	Criteria for testing for type 2 diabetes in children	5
Table 1.3	Fasting and 2-h post-load glucose values for diagnosis of diabetes mellitus and other categories of hyperglycaemia	8
Table 1.4	Prevalence of diabetic dyslipidaemia in Malaysia	21
Table 1.5	Effect of Statin Therapy on CHD: Clinical Events Trials	23
Table 1.6	Outcome of clinical events trials of statin in prevention of new coronary heart disease (CHD) events	25
Table 1.7	Clinical events trials of fibrate drugs involving patients with diabetes	26
Table 1.8	Glycaemic control for non-pregnant individuals with diabetes	30
Table 1.9	Treatment decisions based on LDL cholesterol levels in adults with diabetes mellitus	36
Table 1.10	Order of priorities for treatment of diabetic dyslipidaemia in adults	38
Table 2.1	Method for recruiting diabetic patients	45
Table 3.1	Patient classification by age groups	63
Table 3.2	Classification of patient according to the duration of diabetes	65
Table 3.3	Classification of type 2 diabetic patients by BMI	67

Table 3.4	Classification of type 2 diabetic patients by blood pressure	67
Table 3.5	FPG, A1C and lipid profiles of type 2 diabetic patients	69
Table 3.6	Distributions of patients with microvascular, macrovascular, and microvascular + macrovascular complications of diabetes	70
Table 3.7	Distribution of patients with one, two, three, or four complications	71
Table 3.8	Use of anti diabetic drugs	73
Table 3.9	Use of lipid-lowering drugs	74
Table 3.10	Use of antihypertensive drugs	75
Table 3.11	Distribution of type 2 diabetic patients receiving anti diabetic, lipid-lowering and antihypertensive drugs	76
Table 3.12	Clinical summary of type 2 diabetic patients	79
Table 3.13	Distribution of patients with FPG and A1C values at clinical and not at clinical target	80
Table 3.14	Multiple logistic regression analysis examining the influence of age, duration of diabetes, BMI, ethnicity, and gender on the probability of having A1C levels outside of recommended clinical targets	91
Table 3.15	Distribution of male and female patients with BMI values at clinical and not at clinical targets	93
Table 3.16	Distribution of patients with BMI values at clinical and not at clinical target according to ethnicity	94
Table 3.17	Multiple logistic regression analysis examining the influence of age, duration of diabetes, A1C, ethnicity, and gender on the probability of having BMI levels outside of clinical targets	101

Table 3.18	Distribution of patients with Blood Pressure at clinical targets and not at clinical target in treated and non-treated groups	102
Table 3.19	Multiple logistic regression analysis examining the influence of age, duration of diabetes, BMI, A1C, ethnicity, and gender on the probability of having systolic blood pressure levels outside of recommended clinical targets	121
Table 3.20	Distribution of patients with lipid values at clinical and outside of clinical target in treated (for dyslipidaemia) and non-treated groups of patients	123
Table 3.21	Distribution of patients with total, HDL, LDL cholesterol and triglycerides at clinical and outside of clinical target in treated (for dyslipidaemia) and non-treated groups of patients	125
Table 3.22	Distribution of patients who had none, one, two, three, or all four lipid values outside of clinical targets	127
Table 3.23	Multiple logistic regression analysis examining the influence of age, duration of diabetes, BMI, A1C, ethnicity, and gender on the probability of having total, HDL, LDL cholesterol and triglycerides levels outside of recommended clinical targets	132
Table 3.24	Distribution of patients with high, borderline, and low risk HDL, LDL cholesterol and triglycerides according to ADA classification	134
Table 3.25	Distribution of patients who had none, one, two, or all three lipids values outside of recommended clinical target	137
Table.3.26	Distribution of type 2 diabetic patients with and without the three types of dyslipidaemia	138

Table 3.27	Basic characteristics of type 2 diabetic patients who are not on anti-lipid therapy	139
Table 3.28	FPG, A1C and lipid profiles of type 2 diabetic patients who are not on anti-lipid therapy	141
Table 3.29	Association between lipid parameters among type 2 diabetic patients	148
Table 3.30	Distribution of type 2 diabetic patients according to NCEP ATP III classification	150
Table 3.31	Lipid profile of type 2 diabetic patients with and without dyslipidaemia	151
Table 3.32	Distribution of type 2 diabetic patients with none, one, two, three or four criteria of dyslipidaemia	153
Table 3.33	Distribution of type 2 diabetic patients who are not on anti-lipid therapy with and without the three types of dyslipidaemia	154
Table 3.34	Lipid profile of male and female type 2 diabetic patients	156
Table 3.35	Lipid profile of Malay, Chinese, and Indian subjects	160
Table 3.36	Lipid profile of Malay and non-Malay type 2 diabetic patients	160
Table 3.37	Univariate correlation coefficient and P-values of total, HDL, LDL, VLDL cholesterol and triglycerides against age	162
Table 3.38	Lipid profile of three age groups (< 50 years, 50 – 59 years, and > 59 years) of type 2 diabetic patients	164
Table 3.39	Association between lipid profile and duration of diabetes in type 2 diabetic patients	166
Table 3.40	Lipid profile of type 2 diabetic patients grouped by duration of diabetes	169

Table 3.41	Lipid profile of type 2 diabetic patients with/without family history of diabetes mellitus	170
Table 3.42	Lipid profile of smoker and non-smoker patients	171
Table 3.43	Lipid profile and BMI in type 2 diabetic patients	175
Table 3.44	Lipid profile and three BMI categories (good, acceptable and poor)	180
Table 3.45	Lipid profile and FPG in type 2 diabetic patients	182
Table 3.46	Univariate analyses of lipid profile and A1C	186
Table 3.47	Lipid profile of type 2 diabetic patients with good and poor glycaemic control (at FPG of 7 mmol/L)	191
Table 3.48	Lipid profiles of type 2 diabetic patients with good and poor glycaemic control (at FPG of 8 mmol/L)	192
Table 3.49	Lipid profiles type 2 diabetic patients grouped as FPG < 9 and \geq 9 mmol/L	194
Table 3.50	Lipid profiles of type 2 diabetic patients grouped as FPG < 10 and \geq 10 mmol/L	198
Table 3.51	Lipid profile of patients grouped as A1C < 7 % and \geq 7 %	200
Table 3.52	Lipid profile of patients grouped as A1C < 8 % and \geq 8 %	201
Table 3.53	Lipid profile of patients grouped as A1C < 9 % and \geq 9 %	204
Table 3.54	Lipid profile of patients grouped as A1C < 10 % and \geq 10 %	208
Table 3.55	Lipid profile of type 2 diabetic patients with good, acceptable and poor glycaemic control	213
Table 3.56	Difference in mean lipid profile between three (good, acceptable and poor) glycaemic control groups of patients	214

LIST OF FIGURES

		<u>Page</u>
Figure 1.1	Unstandardized (casual, random) blood glucose values in the diagnosis of diabetes mellitus	7
Figure 1.2	Disorders of glycaemia: aetiological types and clinical stages	10
Figure 1.3	The pathophysiologic basis for diabetic dyslipidemia and its relation to insulin resistance	17
Figure 3.1	Age distribution of type 2 diabetic patients	64
Figure 3.2	Distribution of the duration of diabetes in type 2 diabetic patients	65
Figure 3.3	Distribution of BMI in type 2 diabetic patients	66
Figure 3.4	Distribution of SBP in type 2 diabetic patients	68
Figure 3.5	Distribution of DBP in type 2 diabetic patients	68
Figure 3.6	Types of eye complications in type 2 diabetic patients	72
Figure 3.7	Frequency of male and female subjects with A1C at clinical target and outside of clinical target level	81
Figure 3.8	Distribution of % A1C in Malays and other ethnic groups	82
Figure 3.9	Association of A1C with age	83
Figure 3.10	Mean % A1C of three age groups of patients	84

Figure 3.11	Percentage of patients with A1C level at clinical and outside of clinical target in four groups by duration of diabetes	85
Figure 3.12	Proportions of patients with A1C values at clinical target and outside of clinical target in two groups (with and without positive family history of diabetes)	86
Figure 3.13	Proportion of smoker and non-smoker patients with A1C values at clinical target and outside of clinical target level	87
Figure 3.14	Association between BMI and A1C	88
Figure 3.15	Frequency of the patients with % A1C level at clinical target and outside of clinical target in two BMI groups	89
Figure 3.16	Frequency of the patients with % A1C level at clinical target and outside of clinical target in three BMI groups	90
Figure 3.17	Distribution of BMI in male and female subjects	92
Figure 3.18	Proportion of patients with BMI values at clinical target and outside of clinical target in three age groups	96
Figure 3.19	Mean BMI values of patients in three age groups	96
Figure 3.20	Association of BMI with age	97
Figure 3.21	Association of BMI with duration of diabetes	98
Figure 3.22	Proportion of patients with BMI values at clinical target and outside of clinical target in two groups (with and without positive family history of diabetes)	99
Figure 3.23	Proportion of smoker and non-smoker with BMI values at clinical target and outside of clinical target level	100
Figure 3.24	Frequency of patients with SBP at clinical and outside of clinical target in antihypertensive therapy groups	103

Figure 3.25	Frequency of patients with DBP at clinical and outside of clinical target in antihypertensive therapy groups	104
Figure 3.26	Frequency of male and female subjects with SBP at clinical and outside of clinical target	105
Figure 3.27	Frequency of male and female subjects with DBP at clinical and outside of clinical target	106
Figure 3.28	Frequency of patients with SBP at clinical and outside of clinical target in ethnic groups	107
Figure 3.29	Frequency of patients with DBP at clinical and outside of clinical target in ethnic groups	108
Figure 3.30	Linear association between SBP and age of patients	109
Figure 3.31	Proportion of patients with SBP at clinical and outside of clinical target in three age groups	110
Figure 3.32	Frequency of patients having SBP at clinical and outside of clinical target grouped according to the duration of diabetes	111
Figure 3.33	Frequency of patients having DBP at clinical and outside of clinical target grouped according to the duration of diabetes	112
Figure 3.34	Proportions of patients with SBP at clinical and outside of clinical target in two groups (with positive family history of diabetes and negative family history of diabetes)	113
Figure 3.35	Proportions of patients with DBP at clinical and outside of clinical target in two groups (with positive family history of diabetes and negative family history of diabetes)	114
Figure 3.36	Frequency of smoker and non-smoker patients with SBP at clinical and outside of clinical target level	115

Figure 3.37	Frequency of smoker and non-smoker patients with DBP at clinical and outside of clinical target level	116
Figure 3.38	Frequency of the patients with SBP at clinical and outside of clinical target in two BMI groups	117
Figure 3.39	Frequency of the patients with DBP at clinical and outside of clinical target in two BMI groups	118
Figure 3.40	Frequency of patients with SBP at clinical and outside of clinical target according to glycaemic control	119
Figure 3.41	Frequency of patients with DBP at clinical and outside of clinical target according to glycaemic control	120
Figure 3.42	Frequency of male and female subjects with one, two, three, and four lipid values outside of clinical target	129
Figure 3.43	Frequency of patients with one, two, three, or four lipid values outside of clinical target and good, acceptable, or poor glycaemic control	131
Figure 3.44	Association between FPG and A1C	140
Figure 3.45	Distribution of total cholesterol in type 2 diabetic patients	142
Figure 3.46	Distribution of HDL cholesterol in type 2 diabetic patients	143
Figure 3.47	Distribution of LDL cholesterol in type 2 diabetic patients	144
Figure 3.48	Distribution of VLDL cholesterol in type 2 diabetic patients	145
Figure 3.49	Distribution of triglycerides in type 2 diabetic patients	146
Figure 3.50	Sex distribution in type 2 diabetic patients	155
Figure 3.51	Distribution of total cholesterol in male and female subjects	157
Figure 3.52	Ethnic distribution of type 2 diabetic patients	159
Figure 3.53	Age distribution in type 2 diabetic patients	161

Figure 3.54	Mean LDL cholesterol in age groups < 50 and 50 – 59 years	163
Figure 3.55	Duration of diabetes among type 2 diabetic patients	165
Figure 3.56	Distribution of patients according to the duration of diabetes	167
Figure 3.57	Distribution of BMI in type 2 diabetic patients	172
Figure 3.58	Association between VLDL cholesterol and BMI in type 2 diabetic patients	173
Figure 3.59	Association between triglycerides and BMI	174
Figure 3.60	Distribution of type 2 diabetic patients in three BMI groups	178
Figure 3.61	Distribution of FPG in type 2 diabetic patients	181
Figure 3.62	Association between triglycerides and FPG among type 2 diabetic patients	183
Figure 3.63	Association between total cholesterol and FPG in type 2 diabetic patients	184
Figure 3.64	Association between LDL cholesterol and FPG in type 2 diabetic patients	185
Figure 3.65	Distribution of A1C in type 2 diabetic patients	187
Figure 3.66	Association between A1C and triglycerides	189
Figure 3.67	Distribution of total cholesterol in type 2 diabetic patients based on fasting plasma glucose of 10 mmol/L	195
Figure 3.68	Distribution of mean LDL cholesterol in type 2 diabetic patients based on fasting plasma glucose of 10 mmol/L	196
Figure 3.69	Distribution of mean triglycerides in type 2 diabetic patients based on fasting plasma glucose of 10 mmol/L	197
Figure 3.70	Difference in mean total cholesterol between two groups of patients based on glycaemic control (A1C) of 8 %	202

Figure 3.71	Distribution of LDL cholesterol of type 2 diabetic patients based on glycaemic control (A1C) of 8 %	203
Figure 3.72	Distribution of total cholesterol of type 2 diabetic patients based on glycaemic control (A1C) of 9 %	205
Figure 3.73	Mean LDL cholesterol of type 2 diabetic patients based on glycaemic control (A1C) of 9 %	206
Figure 3.74	Mean triglycerides of type 2 diabetics patients based on glycaemic control (A1C) of 9 %	207
Figure 3.75	Mean total cholesterol of type 2 diabetic patients based on glycaemic control (A1C) of 10 %	209
Figure 3.76	Mean LDL cholesterol of type 2 diabetic patients based on glycaemic control (A1C) of 10 %	210
Figure 3.77	Distribution of triglycerides in type 2 diabetic patients based on glycaemic control (A1C) of 10 %	211
Figure 3.78	Distribution of type 2 diabetic patients in three glycaemic control groups	212
Figure 3.79	Mean total cholesterol of type 2 diabetic patients in three glycaemic control groups (A1C < 7 %, 7 – 10 %, and >10 %)	215
Figure 3.80	Distribution of LDL cholesterol in good, acceptable and poor glycaemic control groups of type 2 diabetic patients	216
Figure 3.81	Mean triglycerides of good, acceptable and poor glycaemic control groups of type 2 diabetic patients	218

LIST OF ABBREVIATIONS

Abbreviation	Full
2-h PG	two-hour postprandial plasma glucose
4S	Scandinavian Simvastatin Survival Study
A1C	glycated hemoglobin (HbA _{1c})
ACE	angiotensin-converting enzyme
ACEI	ACE inhibitor
ADA	American Diabetes Association
ADM	atypical diabetes mellitus
AFCAPS/TexCAPS	Air Force/Texas Coronary Prevention Study
A-II	angiotensin II
ANCOVA	analysis of covariance
ANOVA	analysis of variance
apo	apolipoprotein
apo A-1	apolipoprotein A-1
apo B	apolipoprotein B
ARB	angiotensin receptor blocker
bid	twice a day
BMI	body mass index
BP	blood pressure

bw	body weight
CAD	coronary artery disease
CARE	Cholesterol and Recurrent Events
CCB	calcium channel blocker
CDC	Centers for Disease Control and Prevention
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence intervals
CV	coefficient of variation
CVD	cardiovascular disease
DCCB	Dihydropyridine calcium channel blocker
DCCT	Diabetes Control and Complications Trial
DIGAMI	Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction
ECG	electrocardiogram
EDTA	ethylene diamine tetrachloroacetic acid
ESRD	end-stage renal disease
FBG	fasting blood glucose
FDA	Food and Drug Administration
FFA	free fatty acid
FPG	fasting plasma glucose
FSG	fasting serum glucose
g	gram
GDM	gestational diabetes mellitus

GFR	glomerular filtration rate
HDL	high density lipoproteins
HDLC	HDL cholesterol
HHS	Helsinki Heart Study
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HOPE	Heart Outcomes Prevention Evaluation
hr	hour
HUSM	Hospital Universiti Sains Malaysia
IDDM	insulin dependent diabetes mellitus
IDF	International Diabetes Federation
IDL	intermediate density lipoproteins
IDLC	intermediate density lipoprotein cholesterol
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IPG	impaired plasma glucose
JNC	Joint National Committee
JNC V	Fifth Joint National Committee on Hypertension
JNC VI	Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JODM	juvenile-onset diabetes mellitus
kcal	kilo calorie
kg	kilo gram
LCAS	Lipoprotein and Coronary Atherosclerosis Study
LDL	low density lipoprotein
LDLC	LDL cholesterol

LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
Lp(a)	lipoprotein(a)
LPL	lipoprotein lipase
MBG	mean blood glucose
mg/dl	milli gram per deciliter
MI	myocardial infarction
MICRO-HOPE	Microalbuminuria, Cardiovascular and Renal Outcomes in HOPE
min	minute
mm Hg	milli metre of mercury
mmol/L	milli mol per liter
MNT	medical nutrition therapy
MODY	maturity-onset diabetes of the young
MRI	magnetic resonance imaging
NCEP	National Cholesterol Education Program
NCEP ATP II	NCEP, Adult Treatment Panel II
NCEP ATP III	NCEP, Adult Treatment Panel III
NDCCB	non-DCCB
NDDG	National Diabetes Data Group
NHANES	National Health and Nutrition Examination Survey
NHANES III	Third National Health and Nutrition Examination Survey
NIDDM	Non insulin dependent diabetes mellitus
NPDR	nonproliferative diabetic retinopathy
ODC	Outpatient Diabetes Clinic
OGTT	oral glucose tolerance test

OHA	oral hypoglycemic agent
OR	odds ratio
PCOS	polycystic ovarian syndrome
PDR	proliferative diabetic retinopathy
PG	plasma glucose
PVD	peripheral vascular disease
SD	standard deviation
SDLDL	Small, dense LDL
SENDCAP	the St. Mary 's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study
SI	Système International
SMBG	self-monitoring of blood glucose
SPSS	Statistical Package for Social Sciences
TC	total cholesterol
TG	triglycerides
UAER	urinary albumin excretion rate
UKPDS	United Kingdom Prospective Diabetes Study
VA-HIT	Veterans Affairs–HDL Intervention Trial, or Veteran's Administration HDL Intervention Trial
VLDLC	VLDL cholesterol
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organization
WHR	waist-to-hip circumference ratio
WOSCOPS	West of Scotland Coronary Prevention Study

ABSTRACT

This cross-sectional study was undertaken on 211 type 2 diabetic patients at the Outpatients Diabetes Clinic, HUSM Kubang Kerian, Kelantan between the year 2001 – 2002. The study was conducted to determine whether the clinical targets for the control of diabetes can be met in the context of routine endocrinology practice, and also to define the prevalence of dyslipidaemia, its correlation with glycaemic control and contributing factors. Patients' medical history as well as their family history were obtained using data collection form and physical examination was performed. Samples of patients' venous blood during fasting were taken and analysed for plasma glucose, glycated haemoglobin and lipid profile.

Of the total 211 patients, only 4.3 % were on diet, 37 % of them were on mono therapy while 58.8% were on combination of therapies. There were 46 % patients on lipid-lowering therapy and 54 % on antihypertensive therapy. Analysis showed that many patients had comorbidities or complications. A large number of them had poor glycaemic control (72.5 %). Systolic and diastolic blood pressures of 75.4 % and 84.8 % subjects were ≥ 130 and ≥ 80 mmHg, respectively. BMI values of 66.4 % of the patients were outside the clinical target (BMI ≥ 25 in male and ≥ 24 kg/m² in female). The lipid profile showed that 96.2 % patients had at least one lipid value outside clinical target level. In this study, 70.14 % of the patients had total cholesterol ≥ 5.2 mmol/L, 87.2 % had LDL cholesterol ≥ 2.6 mmol/L, 57.4 % had HDL cholesterol less than the

normal range, ≤ 1.15 mmol/L in men and ≤ 1.4 mmol/L in women, while 45.5 % had triglycerides ≥ 1.71 mmol/L. The most common dyslipidaemic patterns were mixed hyperlipidaemia (36.8 %), followed by hypercholesterolaemia (34.2%) and hypertriglyceridaemia (5.3 %). Complications of diabetes were observed in 47.9 % of the total number of patients.

There were three variables that had significant effects on glycaemic control and they are ethnicity, age and duration of diabetes. Younger Malay subjects (< 50 years old) had significantly the highest mean percent A1C. Patients who were recently diagnosed (duration of diabetes < 5 years) had the best glycaemic control. Variables that had significant effects on BMI were age, duration of diabetes, glycaemic control and gender. Young female and newly diagnosed subjects with good glycaemic control (A1C < 7 %) were found to have higher BMI values. As for the patients' systolic blood pressure, only two factors, namely age and duration diabetes, were found to have significant effects. Aged subjects with a long duration of diabetes were more hypertensive. Based on the study conducted, results showed that glycaemic control and ethnicity were significantly important determinants of elevated total cholesterol, LDL cholesterol and triglycerides levels. Gender and BMI were identified to be significantly important determinants of elevated total cholesterol and triglycerides, respectively.

The overall clinical targets were suboptimal. The prevalence of hyperlipidaemia was high, particularly hypercholesterolaemia. It is imperative that better treatment strategies and methods be adopted to enhance diabetes control and reduce long-term complications of the disease.

ABSTRAK

Faktor faktor yang memberi kesan kepada pengawalan Kawalan diabetes dan dislipidemia di kalangan pesakit diabetes jenis 2 di Hospital Universiti Sains Malaysia

Kajian keratan-lintang ini telah dijalankan terhadap 211 orang pesakit diabetes jenis 2 di Klinik Pesakit Luar, HUSM Kubang Kerian, Kelantan di antara tahun 2001 – 2002. Kajian ini bertujuan menentukan sama ada sasaran klinikal bagi mengawal penyakit diabetes dapat dicapai dalam konteks amalan rutin endokrinologi. Selain itu, kajian ini juga bertujuan mengenal pasti faktor-faktor yang mendorong kepada berlakunya dislipidemia serta perkaitannya antara kawalan tahap glukosa dalam darah. Pemeriksaan fizikal dilakukan terhadap pesakit sementara butir-butir berkenaan dengan kesihatan dan latar belakang pesakit dan keluarga mereka diperolehi dengan cara mengedarkan borang soal selidik. Sampel darah vena pesakit yang dalam keadaan berpuasa telah diambil dan dianalisis untuk menentukan tahap glukosa plasma darah, hemoglobin A1C dan profil lipid.

Hanya 4.3 % daripada keseluruhan 211 orang pesakit mengikut diet pemakanan yang disyorkan, 37 % daripada mereka mengikut satu bentuk terapi sementara 58.8 % mengikut gabungan lebih daripada satu bentuk terapi. Seramai 46 % daripada pesakit ini mengikut terapi untuk menurunkan tahap lipid dan 54 % pula mengikut terapi anti-

hipertensif. Analisis menunjukkan bahawa kebanyakan pesakit mengalami komplikasi diabetes. Sebahagian besar daripada mereka ini tidak mempunyai kawalan glukosa dalam darah yang baik (72.5 %). Seramai 75.4 % daripada pesakit menunjukkan bacaan tekanan darah sistolik ≥ 130 mmHg dan 84.8 % menunjukkan bacaan tekanan darah diastolik ≥ 80 mmHg. Nilai BMI bagi 66.4 % daripada pesakit berada di luar sasaran klinikal (BMI ≥ 25 bagi pesakit lelaki dan ≥ 24 kg/m² bagi pesakit wanita). Profil lipid menunjukkan 96.2 % daripada jumlah pesakit mempunyai sekurang-kurangnya satu nilai di luar daripada tahap sasaran klinikal. Dalam kajian ini, 70.14 % daripada jumlah pesakit mempunyai tahap kolesterol total sebanyak ≥ 5.2 mmol/L dengan 87.2 % mempunyai tahap kolesterol LDL sebanyak ≥ 2.6 mmol/L dan 57.4 % pesakit mempunyai tahap kolesterol HDL kurang dari tahap normal, iaitu ≤ 1.15 mmol/L bagi lelaki dan ≤ 1.4 mmol/L bagi wanita sementara tahap trigliserida bagi 45.5 % daripada mereka berada pada ≥ 1.71 mmol/L. Jenis-jenis dislipidemia yang lazim didapati adalah seperti hiperlipidemia (36.8 %), diikuti dengan hiperkolesterolemia (34.2 %) dan hipertrigliseridemia (5.3 %). Terdapat 47.9 % daripada jumlah pesakit didapati mengalami komplikasi diabetes.

Terdapat tiga pemboleh ubah yang mempunyai kesan yang signifikan terhadap kawalan glukosa dalam darah iaitu faktor etnik, umur dan jangka masa pesakit mengidap diabetes. Pesakit Melayu yang lebih muda (< 50 tahun) mempunyai min peratus hemoglobin A1C yang paling tinggi. Pesakit yang baru saja dikenal pasti mengidap diabetes (jangka masa < 5 tahun) didapati mempunyai kawalan glukosa dalam darah yang lebih baik. Sementara itu, pemboleh ubah yang mempunyai kesan yang signifikan terhadap BMI pula ialah faktor umur, jangka masa pesakit mengidap diabetes, kawalan glukosa dalam darah dan jantina. Pesakit wanita yang lebih muda dan

baru disahkan mengidap diabetes yang mempunyai kawalan glukosa dalam darah yang baik (tahap hemoglobin A_{1c} [A1C] < 7 %) didapati mempunyai nilai BMI yang lebih tinggi. Faktor umur dan jangka masa pesakit mengidap diabetes juga didapati memberi kesan yang signifikan terhadap tekanan darah sistolik pesakit. Pesakit yang lebih tua dan mempunyai jangka masa mengidap diabetes yang lebih lama didapati mempunyai tekanan darah sistolik yang lebih tinggi. Berdasarkan kajian yang dijalankan, keputusan menunjukkan bahawa kawalan glukosa dalam darah dan etnik merupakan dua faktor penting yang mendorong kepada peningkatan tahap kolesterol total, kolesterol LDL dan trigliserida yang signifikan. Jantina dikenal pasti sebagai faktor penting yang mendorong kepada peningkatan tahap kolesterol total manakala BMI mempengaruhi trigliserida.

Kesimpulannya, sasaran klinikal secara keseluruhannya tidak dapat dicapai secara optimum. Hiperlipidemia khususnya hiperkolesterolemia, masih berada pada tahap yang tinggi. Oleh yang demikian, strategi serta kaedah rawatan yang lebih baik seharusnya dilaksana bagi meningkatkan tahap kawalan diabetes dan mengurangkan komplikasi penyakit ini dari segi jangka panjang.

CHAPTER 1
INTRODUCTION

INTRODUCTION

1.1 Prevalence of type 2 diabetes

Type 2 diabetes is the most prevalent form of diabetes, which appears later in life, and it is due to the combination of insulin resistance (impairment in insulin-mediated glucose disposal) and defective secretion of insulin by pancreatic β -cells (Grundy *et. al*, 1999). Diabetes has become one of the most common chronic diseases all over the world. Using American Diabetes Association (ADA) criteria, the Third National Health and Nutrition Examination Survey, 1988 – 1994 (NHANES III) data indicate that diabetes (diagnosed and undiagnosed combined) affects 7.8 % of adults \geq 20 years of age in the U.S., with rates reaching 18.8 % at \geq 60 years of age (Harris *et. al*, 1998). In Latin America, the prevalence of type 2 diabetes is highest among Pima Indians, followed by Hispanics, blacks, and then whites (Ismail & Gill, 1999). The prevalence of diabetes mellitus among Orang Asli was 0.3 % and among Malays was 4.7 % (Ali *et. al*, 1993). Ethnic group, age (\geq 40 years), dietary intake, obesity, and lack of physical activity were associated with higher prevalence of diabetes (Ali *et. al*, 1993; Choi & Shi, 2001). The prevalence of diabetes mellitus and impaired glucose tolerance were 10.5 % and 16.5 % in Kelantan state of north-east Malaysia (Mafauzy *et. al*, 1999). The high prevalence of undiagnosed diabetes and the proportion of cases with evidence of complications at diagnosis undoubtedly create a strong imperative for screening. Between 35 – 50 % cases of diabetes are undiagnosed at any one time. The

prevalence of new cases of diabetes in United Kingdom were 0.2 % (0 % to 1.4 %) and 2.8 % (1.6 % to 4.7 %) in patients whose sole risk factor was age over 45 and in patients aged over 45 with one or more additional risk factors for diabetes, respectively (Lawrence *et. al*, 2001). Up to 25 % of people with diabetes have evidence of microvascular complications at diagnosis, and extrapolation of the association between the prevalence of retinopathy and the duration of disease suggests that the true onset of diabetes occurs several years before it is recognized clinically (Wareham & Griffin, 2001). There are currently 3.5 million people with type 1 diabetes and 119.2 million with type 2 diabetes worldwide, and the number is expected to increase to 5.3 and 212.9 million, respectively in the year 2011 (Bloomgarden, 1998). There have been increases in the prevalence of diabetes from 4 to 8 % in Singapore, from 8 to 16 % in Papua New Guinea, and from 2 to 5 % in Hong Kong (Bloomgarden, 1998). The American Diabetes Association has proposed screening of all people aged over 45 years by measuring fasting blood glucose every three years, in addition to screening patients from high-risk ethnic groups and younger patients with hypertension, obesity, a family history of diabetes in a first degree relative, or a family history of gestational diabetes (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; ADA, 1998c). Criteria for testing for diabetes in asymptomatic, undiagnosed adults are listed in Table 1.1. The recommended screening test for nonpregnant adults is the fasting plasma glucose (ADA, 2002f).

The incidence of type 2 diabetes is increasing in the pediatric population, and presents a serious public health problem. The full effect of this epidemic will be felt as these children become adults and develop the long-term complications of diabetes (Rosenbloom *et. al*, 1999). Until recently, immune-mediated type 1 diabetes was the only type of diabetes and was the most common and increasingly prevalent chronic

diseases in children. Only 1 – 2 % of children were considered to have type 2 diabetes or other rare forms of diabetes. Recent reports indicate that 8 – 45 % of children with newly diagnosed diabetes have nonimmune-mediated diabetes (ADA, 2000b). In US the mean age of children at diagnosis of type 2 diabetes is between 12 and 14 years, corresponding with puberty. The disease affects girls more than boys, predominantly people of non-European origin, and is associated with obesity, physical inactivity, a family history of type 2 diabetes, exposure to diabetes in utero, and signs of insulin resistance (Fagot-Campagna & Narayan, 2001). Criteria for testing for type 2 diabetes in children are listed in Table 1.2.

Table 1.1 Criteria for testing for diabetes in asymptomatic adults

Criteria for testing for diabetes in asymptomatic adult individuals

1. Testing for diabetes should be considered in all individuals at age 45 years and above and, if normal, it should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who
 - are overweight (BMI ≥ 25 kg/m²)
 - have a first-degree relative with diabetes
 - are members of a high-risk ethnic population (e.g., African-American, Latino, Native American, Asian-American, Pacific Islander)
 - have delivered a baby weighing > 9 lb or have been diagnosed with GDM
 - are hypertensive ($\geq 140/90$ mmHg)
 - have an HDL cholesterol level ≤ 35 mg/dl (0.90 mmol/l) and/or a triglycerides level ≥ 250 mg/dl (2.82 mmol/l)
 - on previous testing, had IGT or IFG
 - have other clinical conditions associated with insulin resistance (e.g. PCOS or acanthosis nigricans)

(ADA, 2002f).

Table 1.2 Criteria for testing for type 2 diabetes in children

Testing for type 2 diabetes in children

- Criteria*

Overweight (BMI > 85th percentile for age and sex, weight for height > 85th percentile, or weight > 120% of ideal for height) Plus, Any two of the following risk factors:

1. Family history of type 2 diabetes in first- or second-degree relative
 2. Race/ethnicity (Native American, African-American, Latino, Asian American, Pacific Islander)
 3. Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, or PCOS)
- Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
 - Frequency: every 2 years
 - Test: FPG preferred

*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria (ADA, 2002f).

Diabetes mellitus is a major risk factor for morbidity and mortality due to coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease. Diabetes increases the prevalence of these complications about two to fourfold (ADA, 1989). Metabolic control and duration of type 2 diabetes are important predictors of coronary heart disease (ischemic heart disease) in elderly subjects, particularly in women (Kuusisto *et. al*, 1994). High fasting insulin concentrations are independent predictor of coronary heart disease (ischemic heart disease) in men (Despres *et. al*, 1996). Risk factors for these complications in diabetic patients are the high prevalence of hypertension and lipid abnormalities. Smoking is another risk factor. Other associated risk factors for macrovascular complications are obesity, impaired glucose tolerance, hyperglycaemia, hyperinsulinaemia, microalbuminuria, elevated fibrinogen levels, altered platelet function, and qualitative lipoprotein abnormalities (ADA, 1989).

1.2 Diagnosis of diabetes mellitus

Symptoms of diabetes include polydipsia (increased thirst), polyuria (increased urine volume), recurrent infections, and unexplained weight loss. In severe cases, drowsiness, coma and high levels of glycosuria are usually present. Diabetes can be diagnosed in three ways according to The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002) (Alberti & Zimmet, 1998; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; 2002).

1. Symptoms of diabetes plus casual plasma glucose ≥ 11.1 mmol/L (200 mg/dl) or
2. FPG ≥ 7.0 mmol/L (126 mg/dl) or
3. 2-h PG ≥ 11.1 mmol/L (200 mg/dl) during an oral glucose tolerance test (OGTT).

(i) In persons with symptom of diabetes:

Symptoms of diabetes plus casual plasma glucose ≥ 11.1 mmol/L (200 mg/dl) or FPG ≥ 7.0 mmol/L (126 mg/dl) or 2-h PG ≥ 11.1 mmol/L (200 mg/dl) during an oral glucose tolerance test (OGTT).

(ii) For asymptomatic person, Abnormal tests on two occasions.

The diagnosis needs to be confirmed by repeating the test on a different day. At least one additional plasma glucose test result with a value in the diabetic range is essential, either fasting, from a random (casual) sample, or from the oral glucose tolerance test. A single blood glucose estimation in excess of the diagnostic values indicated in Figure 1.1. However, the oral glucose tolerance test is discouraged for routine clinical use. In epidemiological studies, one fasting plasma glucose measurement will suffice. The World Health Organization (WHO) reserved the use of fasting plasma glucose or 2-hour plasma glucose measurements for epidemiological

purposes and suggested that ideally, both values should be used (Alberti & Zimmet, 1998; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; 2002). Diagnostic interpretations of the fasting and 2-h post-load concentrations in non-pregnant subjects are listed in Table 1.3.

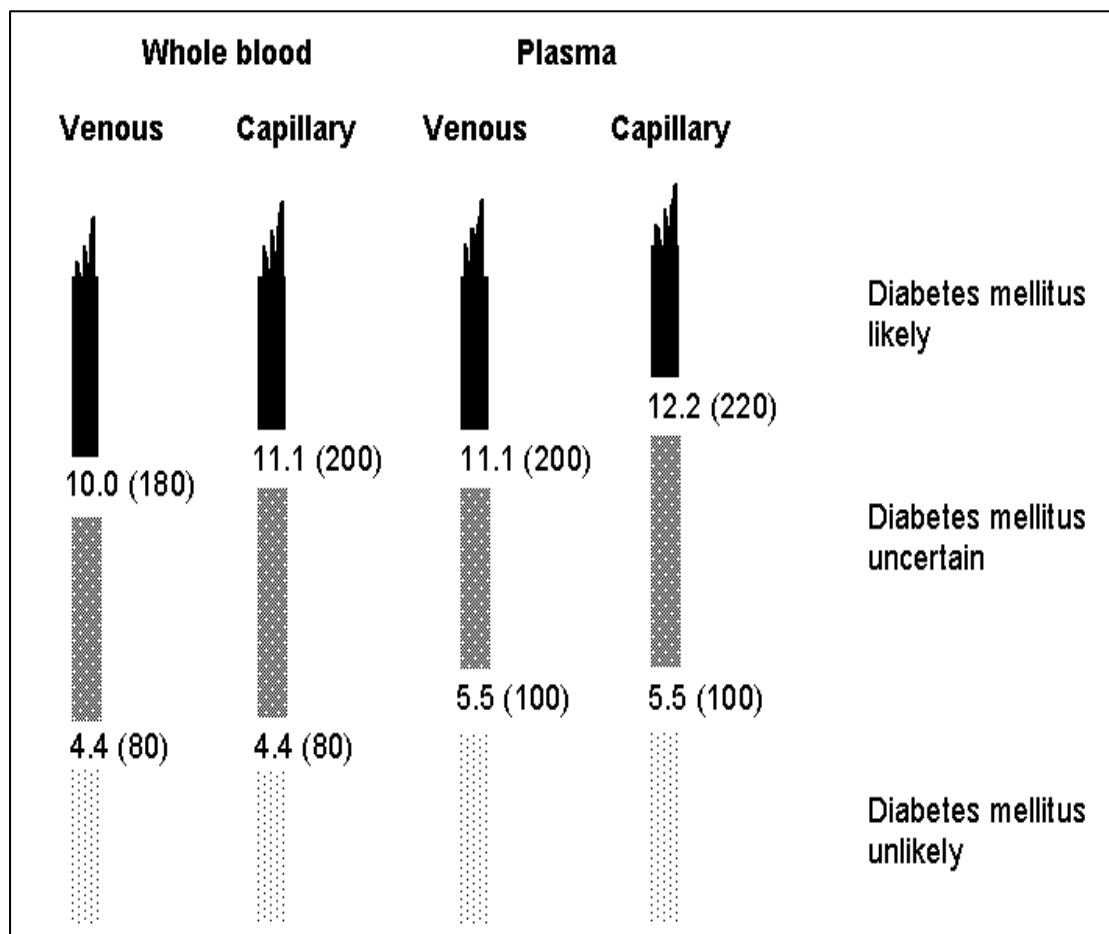


Figure 1.1 Unstandardized (casual, random) blood glucose values in the diagnosis of diabetes mellitus

Values are in mmol/L (mg/dl).

Taken from the WHO Consultation Report (1999).

Table 1.3 Fasting and 2-h post-load glucose values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

Category	Sampling time	Glucose concentration, mmol/L (mg/dl)			
		Whole blood		Plasma	
		Venous	Capillary	Venous	Capillary
Diabetes Mellitus	Fasting *	≥ 6.1 (110)	≥ 6.1 (110)	≥ 7 (126)	≥ 7 (126)
	2-h post glucose load**	≥ 10 (180)	≥ 11.1 (200)	≥ 11.1 (200)	≥ 12.2 (220)
Impaired Glucose Tolerance (IGT)	Fasting *	< 6.1 (110)	< 6.1 (110)	< 7 (126)	< 7 (126)
	2-h post glucose load**	≥ 6.7- <10 (120 - 180)	≥ 7.8 - < 11.1 (140 - 200)	≥ 7.8 - < 11.1 (140 - 200)	≥ 8.9-< 12.2 (160 - 220)
Impaired Fasting Glycaemia (IFG)	Fasting*	≥ 5.6 - < 6.1 (100 - 110)	≥ 5.6 - < 6.1 (100 - 110)	≥ 6.1 - < 7 (110 - 126)	≥ 6.1 - < 7 (110 - 126)
	2-h post glucose load**	< 6.7 (120)	< 7.8 (140)	< 7.8 (140)	< 8.9 (160)

Taken from the WHO Consultation Report (1999).

* 10 – 12 hours

** 75 gr oral glucose load

Values are for non-pregnant subjects.

1.3 Classification of diabetes mellitus

With a better understanding of the pathophysiology and regulation of glucose metabolism, new classifications of diabetes based on aetiologies and clinical staging (Figure 1.2) have been recommended by the World Health Organization (Alberti & Zimmet, 1998; WHO Consultation, 1999) and the American Diabetes Association (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; 2002). Both the reports of the American Diabetes Association and the World Health Organization recommend altering the classification to define four main subtypes of diabetes.

1. Type 1 diabetes (previously called insulin-dependent diabetes mellitus [IDDM] or juvenile-onset diabetes mellitus [JODM]) represents clinically about 5 percent of all persons with diagnosed diabetes. Its clinical onset is typically at ages under 30 years. It is an autoimmune or idiopathic destructive disease in beta (insulin-producing) cells of the pancreas in genetically susceptible individuals, which leads to absolute insulin deficiency. The clinical onset of Type 1 diabetes may be more gradual after age 30. Insulin therapy is always required for both life and diabetes control.

2. Type 2 diabetes (previously called non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes [AODM]), which may originate from insulin resistance and relative insulin deficiency or from a secretory defect. Type 2 diabetes is the most common form of diabetes in the world, especially in minority communities and the elderly. Approximately 95 % of all persons with diagnosed diabetes and 100 % of undiagnosed diabetes have type 2 diabetes.

Type of diabetes mellitus	Normoglycaemia	Hyperglycaemia			
			Diabetes mellitus		
	Normal glucose tolerance	IGT* and/or IFG †	Not requiring insulin	Requiring insulin for control	Requiring insulin for survival
<i>Type 1</i> Autoimmune Idiopathic					
<i>Type 2</i> Predominantly insulin resistance Predominantly insulin secretory defects					
<i>Other specific types ‡</i>					
<i>Gestational diabetes ‡</i>					

Figure 1.2 Disorders of glycaemia: aetiological types and clinical stages

* IGT impaired glucose tolerance, † IFG impaired fasting glycaemia, ‡ In rare instances, patients in these categories (e.g. type 1 diabetes mellitus during pregnancy) may require insulin for survival

Taken from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002).

3. Other specific types: it covers a wide range of specific types of diabetes including the various genetic defects of beta cell function, genetic defects in insulin action, diseases of the exocrine pancreas and medication use.

- (a) Genetic defects of β -cell function (e.g. maturity onset diabetes of youth types 1 – 6)
- (b) Genetic defects in insulin action (e.g. type A insulin resistance)
- (c) Diseases of the exocrine pancreas (e.g. pancreatitis, haemochromatosis)
- (d) Endocrinopathies (e.g. acromegaly, Cushing's syndrome)
- (e) Drug or chemical induced (e.g. thiazides, glucocorticoids)
- (f) Infections (e.g. congenital rubella)
- (g) Uncommon forms of immune-mediated diabetes (e.g. 'stiff man' syndrome)
- (h) Other genetic syndromes sometimes associated with diabetes (e.g. Down's syndrome, Lawrence-Moon-Biedel syndrome)

4. Gestational Diabetes Mellitus (GDM): it is the recognition of hyperglycemia during pregnancy in an individual not previously known to have diabetes. Approximately 3 percent of all pregnancies are associated with Gestational Diabetes Mellitus. Gestational Diabetes Mellitus identifies health risks to the fetus/newborn and future diabetes in the mother.

1.4 Hyperglycemia

Type 2 diabetes is a progressive disease associated with numerous serious complications that develop over time. Patients with type 2 diabetes are at increased risk for cardiovascular disease. These complications are directly and strongly related to hyperglycemia (Stratton *et. al*, 2000). Hyperglycemia affects biochemical parameters and influences the progression of coronary heart disease and mortality rates in diabetic patients. Aggressive treatment to control hyperglycemia is much more effective in reducing the number of complications than standard treatment (Van der does *et. al*, 1998; Herman, 1999). In the Paris Prospective Study, in the upper levels of glucose distributions, the risk of death progressively increased with increasing fasting and 2-h glucose concentrations. There were no clear thresholds for fasting or 2-h glucose concentrations above which mortality sharply increased (Balkau *et. al*, 1999).

1.4.1 Fasting Plasma Glucose

Impaired fasting plasma glucose or impaired glucose tolerance is the first abnormality in plasma glucose seen in patients with insulin resistance (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Many prospective studies (Rewers *et. al*, 1992; Haffner, 1997; Goldberg *et. al*, 1998; Coutinho *et. al*, 1999) show that impaired fasting plasma glucose or impaired glucose tolerance is a risk factor for cardiovascular diseases. The risk of developing cardiovascular diseases is greater in people with both impaired glucose tolerance and impaired fasting plasma glucose (Lim *et. al*, 2000). The degree of independence as a risk factor, however, is uncertain, because impaired fasting plasma glucose commonly coexists with other components of the metabolic syndrome (Haffner *et. al*, 1990). A patient with impaired fasting plasma glucose or impaired glucose tolerance are at risk for both cardiovascular diseases and type 2 diabetes (Rewers *et. al*, 1992). Once categorical hyperglycemia or

diabetes develops, it counts as an independent risk factor for cardiovascular disease (Wilson, 1998). There is a direct relationship between the degree of plasma glucose control and the risk of microvascular complications of both type 1 (Diabetes Control and Complications Trial [DCCT] Research Group, 1993) and type 2 (U.K. Prospective Diabetes Study [UKPDS] Group, 1998e) diabetes. Type 1 diabetic patients with lower average plasma glucose concentrations had a significantly lower incidence of microvascular complications, but reduction in the risk of macrovascular complication was not significant (DCCT Research Group, 1993), and 34 % reduction in hypercholesterolemia was observed with intensive insulin therapy. Similar results were observed in type 2 diabetic patients (UKPDS Group, 1998e). Poor prognosis is directly related to higher glucose concentrations. For example, the 10-year survival was reduced if fasting plasma glucose was ≥ 7.8 mmol/L. The risk of death was significantly increased for patients with fasting plasma glucose ≥ 7.8 mmol/L. Type 2 diabetic patients with fasting plasma glucose ≥ 7.8 mmol/L had increased cardiovascular mortality and a moderately increased in FPG was a risk factor for myocardial infarction (Andersson & Svardsudd, 1995).

1.4.2 Glycated hemoglobin

Glycated hemoglobin is formed from the slow, non-enzymatic reaction between glucose and hemoglobin (Bun, 1981). For hemoglobin, the rate of synthesis of glycated hemoglobin is principally related to the concentration of plasma glucose. Measurement of glycated proteins, primarily glycated hemoglobin, is widely used for routine monitoring of long-term glycaemic status in patients with diabetes mellitus. Glycated hemoglobin is a clinically useful index of mean glycaemia during the preceding 120 days, the average life span of erythrocytes (Bunn, 1981; Jovanovic & Peterson, 1981;

Nathan *et. al*, 1984; Cefalu *et. al*, 1994; Goldstein *et. al*, 1995). In most studies glycated hemoglobin was used to evaluate glycaemic control, rather than glucose concentration. Moreover, most clinicians use the American Diabetes Association recommendations, which define a target glycated hemoglobin concentration as the goal for optimum glycaemic control. The predicted incidence of nonproliferative (background) diabetic retinopathy (NPDR), proliferative diabetic retinopathy, macular edema and blindness were reduced by 66 %, 94 %, 71 % and 72 % in comprehensive care compared with standard care. Comprehensive care reduced nephropathy outcomes by 39 % (microalbuminuria) and 87 % (proteinuria, ESRD) and reduced neuropathy outcomes by 68 % (symptomatic distal polyneuropathy) and 67 % (lower extremity amputation)(Eastman *et. al*, 1997). Glycated hemoglobin concentration seems to explain most of the excess mortality risk of diabetes in men and to be a continuous risk factor through the whole population distribution (Khaw *et. al*, 2001). The incidences of mortality attributed to coronary heart disease and all coronary heart disease events increased significantly in patients with glycated hemoglobin concentrations in the highest tertile (> 7.9 %) compared with patients with glycated hemoglobin concentrations lower than 6 % (Kuusisto *et. al*, 1994). Each 1 % reduction in glycated hemoglobin was associated with reductions in risk of ≥ 45 % for the progression of diabetic retinopathy (DCCT Research Group, 1995), 21 % for any end point related to diabetes, 21 % for deaths related to diabetes, 14 % for myocardial infarction, and 37 % for microvascular complications (Stratton *et. al*, 2000).

1.5 Diabetic dyslipidaemia

The term hyperlipidaemia refers to an increase in concentration of one or more plasma or serum lipids, usually cholesterol and triglycerides and the term dyslipidaemia is used for either an increase or decrease in concentration of one or more plasma or serum lipids. Cholesterol and triglycerides are transported in the blood in the form of lipoproteins. Plasma total cholesterol in human is distributed among three major lipoprotein classes: very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Smaller amounts of cholesterol are also contained into minor lipoprotein classes: intermediate density lipoproteins (IDL) and lipoprotein (a) [Lp (a)]. LDL carry most of the circulating cholesterol (60 – 70 % of total cholesterol). HDL contain 20 – 30 % of the total cholesterol and they play a major role in reverse cholesterol transport. The dietary triglycerides are transported in chylomicra from its intestinal site of absorption into the systemic circulation. The endogenously synthesized triglycerides are transported in VLDL. The desirable lipid profile (total, HDL, LDL cholesterol and triglycerides) is as follow: Total cholesterol < 5.2 mmol/L or triglycerides < 1.71 mmol/L, low-density lipoprotein (LDL) < 2.6 mmol/L and high-density lipoprotein (HDL) \geq 1.15 mmol/L. A subject is considered dyslipidaemic when one of the above criteria is fulfilled (The National Cholesterol Education Program, 2001; ADA, 2002d). The study of lipid profile is necessary in diagnosis and treatment of dyslipidaemia.

The pathophysiology of underlying diabetic dyslipidemia is closely linked to insulin resistance, which in turn leads to increased release of fatty acids from adipose tissue (Nikkila & Kekki, 1973; Frayne *et. al*, 1996). Increased plasma levels of fatty acids increase production of VLDL, TG, and cholesterol by the liver (Nikkila & Kekki, 1973; Frayne *et. al*, 1996).). Increased plasma TG levels are then the “driving force” for low HDLC and abnormal, small dense LDL (Reaven *et. al*, 1993; Griffin *et. al*, 1994; Tan *et. al*, 1995). The pathophysiologic basis for diabetic dyslipidemia and its relation to insulin resistance is presented in Figure 1.3. In the first, we see that insulin-resistant fat cells undergo greater breakdown of their stored triglycerides and greater release of free fatty acids into the circulation (Nikkila & Kekki, 1973; Frayne *et. al*, 1996). This is a common abnormality seen in both obese and nonobese insulin-resistant subjects and those with type 2 diabetes (Goldberg, 2001). Increased fatty acids in the plasma leads to increase fatty acid uptake by the liver. The liver takes those fatty acids and synthesizes them into triglycerides (Nikkila & Kekki, 1973; Frayne *et. al*, 1996). The presence of increased triglycerides stimulates the assembly and secretion of the apolipoprotein (apo) B and very low density lipoprotein (Goldberg, 2001). The result is an increased number of VLDL particles and increased level of triglycerides in the plasma, which leads to the rest of the diabetic dyslipidemic picture. In the presence of increased VLDL in the plasma and normal levels of activity of the plasma protein cholesteryl ester transfer protein (CETP), VLDL triglycerides can be exchanged for HDL cholesterol. That is, a VLDL particle will give up a molecule of triglyceride, donating it to the HDL, in return for one of the cholesteryl ester molecules from HDL (Channon *et. al*, 1990; Bhatnagar *et. al*, 1992). This leads to two outcomes: a cholesterol-rich VLDL remnant particle that is atherogenic, and a triglyceride-rich cholesterol-depleted HDL particle. The triglyceride-rich HDL particle can undergo further modification including hydrolysis of

its tryglyceride, probably by hepatic lipase, which leads to the dissociation of the structurally important protein apo A-I. The free apo A-I in plasma is cleared more rapidly than apo A-I associated with HDL particles. In this situation, HDL cholesterol is reduced, and the amount of circulating apo A-I and therefore the number of HDL particles is also reduced (Caslake *et. al*, 1992). A similar phenomena leading to small, dense LDL. Increased levels of VLDL triglyceride in the presence of CETP can promote the transfer of triglyceride into LDL in exchange for LDL cholesteryl ester (Channon *et. al*, 1990; Bhatnagar *et. al*, 1992). The triglyceride-rich LDL can undergo hydrolysis by hepatic lipase or lipoprotein lipase, which leads to a small, dense, cholesterol-depleted—and, in general, lipid-depleted—LDL particle (Caslake *et. al*, 1992).

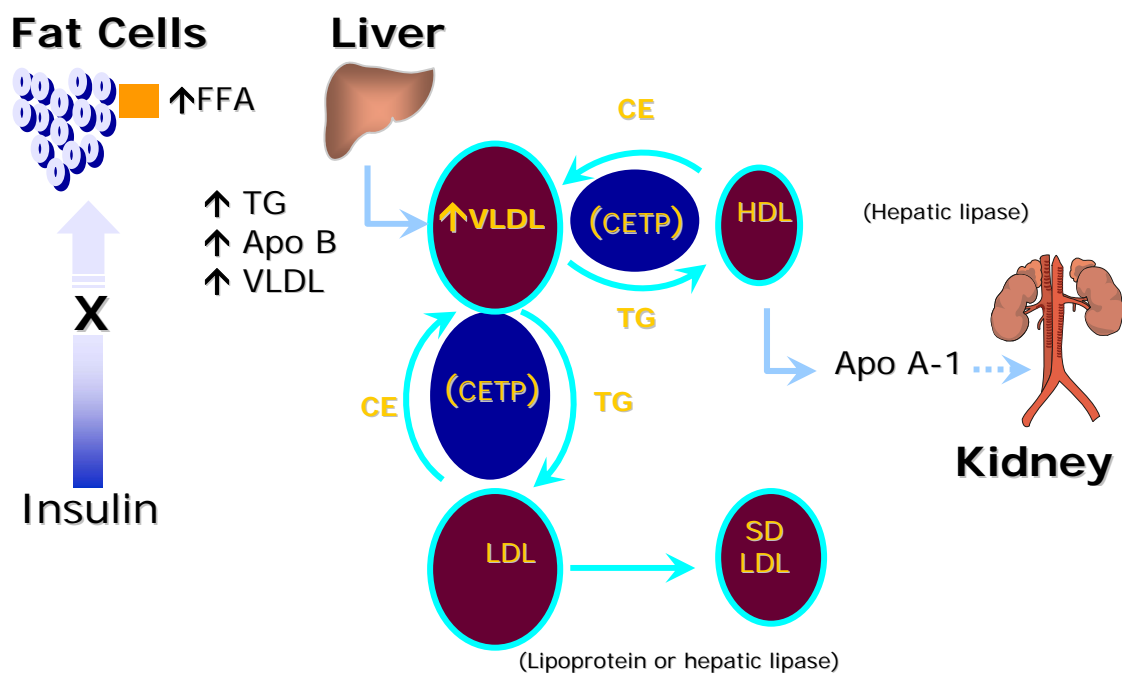


Figure 1. 3 The pathophysiologic basis for diabetic dyslipidemia and its relation to insulin resistance

Small, dense LDL appears to be more susceptible to oxidative modification (Chait *et. al*, 1993; Dejager *et. al*, 1993). Because they are smaller, these particles appear to penetrate the endothelial layer of the arterial wall more easily. The apo B molecule in small, dense LDL undergoes a conformational change that leads to decreased affinity for the LDL receptor, therefore allowing this LDL particle to remain in the circulation longer and be more liable to oxidative modification and uptake into the vessel wall. Finally, in population studies and small clinical studies, small, dense LDL is associated with the insulin-resistance syndrome as well as with high triglycerides and low HDL cholesterol (Austin & Edwards, 1996). There are a number of reasons to consider hypertriglyceridemia as at least a marker of increased atherogenic potential. First of all, hypertriglyceridemia is associated with the accumulation of chylomicron remnants, which we know can be atherogenic, and accumulation of VLDL remnants, which are also atherogenic. As previously discussed, hypertriglyceridemia generates small, dense LDL and is the basis for low HDL in the general population. Hypertriglyceridemia is also associated with increased coagulability and decreased fibrinolysis, as shown by its association with increased levels of plasminogen activator inhibitor 1 (PAI-1) and factor VII and its activation of prothrombin to thrombin (Austin & Edwards, 1996).

People with diabetes frequently have elevated levels of triglycerides, whereas HDL-cholesterol levels are lower than in people without the disease (Dean *et. al*, 1996). Poor glycaemic control worsens lipid abnormalities associated with type 2 diabetes (Dean *et. al*, 1996). In addition, diabetic nephropathy and obesity contribute to adverse changes in the plasma lipid pattern (Dean *et. al*, 1996). The central characteristic of dyslipidaemia in patients with type 2 diabetes is an elevated triglycerides level, particularly triglycerides-rich VLDL levels and decreased HDL cholesterol levels

(ADA, 2002d). In diabetic patients, the concentration of LDL cholesterol is usually not significantly different from that seen in non-diabetic individuals (ADA, 2002d). However, patients with type 2 diabetes typically have a preponderance of smaller, denser, oxidized LDL particles, which may increase atherogenicity (Lamarche *et. al*, 1997; ADA, 2002d), even if the absolute concentration of LDL cholesterol is not elevated. This lipid triad, referred to as atherogenic dyslipidaemia, is usually present in patients with premature coronary artery disease. Atherogenic dyslipidaemia (diabetic dyslipidaemia) is characterized by 3 lipoprotein abnormalities: elevated very-low-density lipoproteins (VLDL), small LDL particles, and low high-density-lipoprotein (HDL) cholesterol (the lipid triad). (Grundy, 1997; Grundy *et. al*, 1999). This shift in lipid levels increases the risk to develop coronary heart disease (Koskinen *et. al*, 1992; Manninen *et. al*, 1992; Gardner *et. al*, 1996). The presence of increased triglycerides and decreased HDL levels are the best predictor of cardiovascular disease in patients with type 2 diabetes (Laakso *et. al*, 1993). Most recently, results of the Strong Heart Study indicate that LDL cholesterol is an independent predictor of cardiovascular disease in patients with diabetes, along with age, albuminuria, fibrinogen, HDL cholesterol (inverse predictor), and percent body fat (inverse predictor) (Howard *et. al*, 2000). Starting with LDL levels as low as 1.82 mmol/L (70 mg/dl), every 0.26 mmol/L (10 mg/dl) increase in LDL cholesterol was associated with a 12 % increase in risk of cardiovascular disease. This finding is supported by results of prospective, long-term clinical trials in which reduction of LDL levels was associated with a significantly reduced risk of cardiovascular events in both diabetic and non-diabetic participants (Goldberg *et. al*, 1998). In an analysis from the Framingham Heart Study (Garg & Grundy, 1990), lipid levels in men and women with and without diabetes were compared to levels in the overall U.S. population. For total cholesterol and LDL

cholesterol, there were no differences between normal and diabetic men or between normal and diabetic women. However, the diabetic men and women had about twice the prevalence of low HDL cholesterol levels and about twice the prevalence of high triglyceride levels as did their nondiabetic counterparts. Results from the Strong Heart Study (Howard, 1998) help to explain why the Framingham data show relatively higher rates of CHD mortality in diabetic women than diabetic men. Among women, HDL cholesterol was approximately 8 mg/dl lower in diabetics compared with nondiabetics, whereas among men, HDL cholesterol was about 4 mg/dl lower in diabetics compared with nondiabetics. A comparison of LDL particle size also indicates a relatively greater decrease with diabetes among women compared with men. In a comparison of diabetic men and women from the United Kingdom Prospective Diabetes Study (UKPDS, 1997) and normal healthy control subjects, total cholesterol levels did not differ between the diabetics and the control subjects. For LDL cholesterol, there was also no difference among the men; however, women with type 2 diabetes in UKPDS had slightly but significantly higher LDL cholesterol levels than their normal counterparts. The data are more striking, however, for both HDL cholesterol, which was lower in the diabetics for both genders, and for triglycerides, which were higher in the diabetic subjects than in the normal control subjects.

About 97 % of adults with diabetes have one or more lipid abnormalities (Henry, 2001). In the San Antonio Heart Study more than 40 % of diabetic patients were hyperlipidaemic and an additional 23 % had hypertriglyceridaemia and/or low level of HDL cholesterol (Stern *et. al*, 1989). High or borderline-high total cholesterol were observed in 70 % of the individuals with diagnosed diabetes, and 77 % of those with undiagnosed diabetes (Harris, 1991). Finnish investigators reported a 53 % prevalence of hypercholesterolemia (plasma cholesterol > 6.5 mmol/l) in a non-insulin-dependent

diabetes mellitus cohort, which was similar to the prevalence in the corresponding non-diabetic population (Rönnemaa *et. al.*, 1989). Despite the high and widespread prevalence of dyslipidaemia among people without and with diabetes, only 2.2 % (Primatesta & Poulter, 2000) of adults without diabetes and 32 % (Henry, 2001) of diabetic patients are receiving treatment with diet, exercise, or drugs to reduce lipid levels and less than one third of patients with established cardiovascular disease received such treatment. (Primatesta & Poulter, 2000). Furthermore, among those who are being treated, only 1 % have reached the ADA goal of LDL < 2.6 mmol/L (100 mg/dl) (Henry, 2001). The prevalence and patterns of diabetic dyslipidaemia among type 2 diabetic patients in Malaysia is summarized in Table 1.4.

Table 1.4 Prevalence of diabetic dyslipidaemia in Malaysia

Mohamad et al., 1997 (70 type 2 diabetic patients)	
Hypercholesterolaemia (≥ 6.1 mmol/L)	80 %
Hypertriglyceridaemia (≥ 2.7 mmol/L)	58 %
Hyper LDL-cholesterolaemia (≥ 4 mmol/L)	68.5 %
Low HDL-cholesterolaemia (< 0.9 mmol/L)	17.6 %
Mafauzy et al., 1999 (diabetic)	
Hypercholesterolaemia (≥ 5.2 mmol/L)	71.9 %
Mixed hyperlipidaemia (TC ≥ 5.2 and TG ≥ 2.3)	23 %
Ismail et al., 2001 (type 2 diabetic patients)	
Hypercholesterolaemia (> 5.2 mmol/L)	73.2 %
Hypertriglyceridaemia (> 2.3 mmol/L)	27.3 %
Hyper LDL-cholesterolaemia (> 2.6 mmol/L)	90.9 %
Low HDL-cholesterolaemia (< 1.15 mmol/L)	52.6 %

Type 2 diabetic patients have markedly increased risk of coronary heart disease than similarly dyslipidaemic non diabetic subjects (Koskinen *et. al*, 1992). Low HDL and HDL₂ cholesterol, high VLDL cholesterol, and high total and VLDL triglycerides are powerful risk indicators for coronary heart disease events in patients with non-insulin-dependent diabetes mellitus (Laakso *et. al*, 1993). LDL size is associated inversely and prospectively with the incidence of coronary artery disease (Gardner *et. al*, 1996). Serum triglycerides concentration has prognostic value, both for assessing coronary heart disease risk and in predicting the effect of Gemfibrozil treatment, especially when used in combination with HDL and LDL cholesterol (Manninen *et. al*, 1992). Cholesterol-lowering therapy will be beneficial for the majority of patients with coronary disease who have average cholesterol levels (Sacks *et. al*, 1996). The incidences of coronary heart disease mortality and all coronary heart disease events were significantly related to total cholesterol and total triglycerides. Furthermore, HDL cholesterol was significantly and inversely related to both coronary heart disease mortality and all coronary heart disease events (Lehto *et. al*, 1997). Baseline data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that both decreased HDL and elevated LDL cholesterol predicted coronary heart disease (Turner *et. al*, 1998). HDL cholesterol concentration is inversely correlated with risk of coronary heart disease and low HDL cholesterol concentration is a strong and important independent predictor of coronary heart disease.

Drugs were developed that lowered circulating cholesterol concentrations and the drugs were tested in clinical trials. Results of these trials showed that lowering LDL cholesterol reduced the risk of morbid and mortal coronary events (Table1.5). Two major classes of lipid-lowering agents, the statins (3-hydroxy-3-methylglutaryl

coenzyme A [HMG CoA] reductase inhibitors) and fibrates (fibric acid derivatives), are available. Nicotinic acid, because of its deleterious effect on glucose tolerance, and bile acid binding resins, because of their triglycerides-elevating properties, are not first-choice agents in patients with non-insulin-dependent diabetes mellitus (Tikkanen *et. al*, 1998). Simvastatin had powerful LDL cholesterol and total cholesterol-lowering efficacy in both plasma lipid phenotypes and can be recommended for treatment of both types of hyperlipidaemia (combined hyperlipidaemia and isolated hypercholesterolaemia) in non-insulin-dependent diabetes mellitus patients. Gemfibrozil, which had no effect on LDL cholesterol in combined hyperlipidaemia but effectively lowered triglycerides levels, can be used in patients with high triglycerides and normal or low LDL cholesterol levels (Tikkanen *et. al*, 1998).

Table 1.5 Effect of Statin Therapy on CHD: Clinical Events Trials

Trial	Baseline LDLC‡	↓LDLC‡	LDLC ‡ Achieved	Statin Event* Rate	Placebo Event* Rate	RRR
4S	188	35%	122	19.4%	28.0%	34%
LIPID	150	25%†	112	12.3%	15.9%	24%
CARE	139	32%	98	10.2%	13.2%	24%
WOSCOPS	192	26%	159	5.3%	7.5%	29%
AFCAPS	150	25%	115	3.5%	5.5%	37%

*Nonfatal MI or CHD death in WOSCOPS, CARE, LIPID; nonfatal or fatal MI, unstable angina, or sudden cardiac death as first event in AFCAPS; nonfatal MI, coronary death, or resuscitated cardiac arrest in 4S.

†vs. placebo, ‡ (mg/dl)

Reduction in recurrent coronary heart disease events in diabetic patients in the Scandinavian Simvastatin Survival Study (4S), (Scandinavian Simvastatin Survival Study Group, 1994; Pyorala *et. al*, 1997), the Cholesterol and Recurrent Events (CARE) trial, (Sacks *et. al*, 1996; Goldberg *et. al*, 1998) and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)(The Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] Study Group, 1998) clinical trials were associated with aggressive LDL-lowering therapy (Table 1.6). In the Scandinavian Simvastatin Survival Study (4S) trial, Simvastatin (HMG CoA reductase inhibitor or “statin”) significantly reduced coronary heart disease incidence and total mortality (borderline significantly) in diabetic subjects with high LDL cholesterol and with previous clinical coronary heart disease. In the Cholesterol and Recurrent Events (CARE) study (Sacks *et. al*, 1996), Pravastatin reduced coronary heart disease incidence significantly in diabetic subjects with average LDL cholesterol levels and with previous clinical coronary heart disease. Patients without previous MI were studied in the West of Scotland Coronary Prevention Study (WOSCOPS) (Shepherd *et. al*, 1995), which examined patients with severe hypercholesterolemia, and the Air Force/Texas Coronary Prevention Study (AFCAPS/TexCAPS) (Downs *et. al*, 1998), which studied patients with average cholesterol. Trials showed that lipid lowering with a statin prevents clinical events, and with each study, the pool of patients proven to benefit was expanded. In the Helsinki Heart Study (Koskinen *et. al*, 1992), Gemfibrozil (fibric acid derivative) was associated with a reduction in coronary heart disease in diabetic subjects without prior coronary heart disease (although this result was not statistically significant) (Table 1.7).

Table 1.6 Outcome of clinical events trials of statin in prevention of new coronary heart disease (CHD) events

	Effect of statin on CHD risk (%)	Level of significance
<u>Secondary prevention</u>		
4S		
All participants (N = 4444)	- 34	<i>P</i> < 0.00001
Diabetes (n = 202)	- 55	<i>P</i> = 0.002
Diabetes (new definition, n = 483)	- 42	<i>P</i> = 0.001
IGT (n = 675)	- 40	<i>P</i> = 0.001
CARE		
All participants (N = 4159)	- 24	<i>P</i> = 0.003
Diabetes (n = 586)	- 25	<i>P</i> = 0.05
LIPID		
All participants (N = 9014)	- 24	<i>P</i> < 0.001
Diabetes (n = 782)	- 19	NS
<u>Primary prevention</u>		
WOSCOPS		
All participants (N = 6595)	- 31	<i>P</i> < 0.001
Diabetes (n = 76)	Numbers too small for analysis	
AFCAPS/TexCAPS		
All participants (N = 6605)	- 37	<i>P</i> < 0.001
Diabetes (n = 155)	Numbers too small for analysis	

Table 1.7 Clinical events trials of fibrate drugs involving patients with diabetes

Helsinki Heart Study	Change in CHD risk on active treatment in 5 years
Whole study (4081 participants)	- 34% P < 0.02
Diabetes (135 participants)	- 68% (total events = 10) NS
SENDCAP (Elkeles, <i>et. al</i>, 1998)	Change in CHD risk on active treatment in 3 years
Diabetes (164 participants)	- 67 % P = 0.01

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), Gemfibrozil was associated with a 24 % decrease in cardiovascular events in diabetic subjects with prior cardiovascular disease (Rubins *et. al*, 1999). In the Lipoprotein and Coronary Atherosclerosis Study (LCAS) 339 patients with mildly to moderately elevated LDL cholesterol (68 had baseline HDL cholesterol > 0.91 mmol/L, mean 0.82 ± 0.06 mmol/L versus 1.23 ± 0.29 mmol/L in 271 patients with baseline HDL cholesterol ≤ 0.91 mmol/L), were randomized for placebo and Fluvastatin treatment to compare angiographic progression and the benefits of the Fluvastatin in patients with low versus patients with higher HDL cholesterol. In placebo group, patients with low HDL cholesterol had significantly more angiographic progression than patients with higher HDL cholesterol. Angiographic progression was significantly reduced among low-HDL cholesterol patients than higher-HDL cholesterol patients in the treatment group (Ballantyne *et. al*, 1999). Each 1 mg/dl increase in HDL cholesterol was associated with 2 % (men) and 3 % (women) reduction in risk for coronary artery disease events (Gordon *et. al*, 1989; Ballantyne *et. al*, 1999; Howard *et. al*, 2000).