Risk factors for long term complications among patients of endocrine clinic in Hospital Penang, Malaysia

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Abstract

Introduction: The prevalence of diabetes is on the increase and an estimated 239 million people worldwide are expected to have the condition by the year 2020 (1). Diabetes mellitus (DM) represents a serious health care challenge. The aim of the study was to evaluate the patient clinical characteristics and risk factors for long term complications in the endocrine clinic of Hospital Penang, Malaysia.

Methods: Descriptive Prospective cross-sectional study design was chosen. To achieve a power of 0.7 with alpha set at 0.05, 186 subjects were required for the study but researcher increase the sample to 297 in case of drop out. Self-developed data collection form was used to collect the patient information.

Results: 297 (100%) patients were enrolled from OPD diabetic clinic of Hospital Palau Pinang. Among the sample 150 (50.5%) were males and rest 147 (49.5%) females. Malay males mean weight at the time of diagnosis significantly higher (p<0.001,) as compared to other ethnics, same results found among Malay females (p<0.001). Findings suggested increased number of risk factors among the study population. Finding also showed that hypertension found among all the classes of diagnosis. Significant variable are diagnosis class and medication consideration.

Conclusion of the study suggested that majority of patients are at high risk of long-term complications and comorbidies. It has been found that increased rate of risk factors have been found among the study population and non-significant to sociodemographic differences.

Keywords: diabetes mellitus, risk factors, long term complications, endocrine clinic, clinical health.

Introduction

The prevalence of diabetes is on the increase and an estimated 239 million people worldwide are expected to have the condition by the year 2020 (1). Diabetes mellitus (DM) represents a serious health care challenge. It is a heterogeneous disorder characterized by varying degrees of insulin resistance and insulin deficiency, which leads to disturbances in glucose homeostasis. It is commonly associates with prolonged ill health and premature death (2). The mortality rate in patients with DM may be up to eleven times higher than in persons without the disease (3, 4). DM is the leading cause of blindness, renal failure and foot and leg amputations in adults in developed countries (1). The World Health Organization (WHO) classification system of DM recognized two major forms of diabetes (5); Type 1 diabetes mellitus (DM), formerly known as insulin dependent diabetes mellitus (IDDM; patient is dependent on exogenous insulin for survival) and Type 2 DM, formerly known as non-insulin dependent diabetes mellitus (NIDDM; patient is not necessary dependent on exogenous insulin for survival). Teamwork and collaboration are essential components of successful DM management, both to prevent complications and maintain the patients' health-related quality of life (HRQOL) over a

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lifetime of coping with the disease (1). Type 1 DM is characterized by insulin deficiency resulting from immune-mediated pancreatic beta-cell destruction. The most serious acute consequence of this is ketoacidosis. Pancreatic beta-cell destruction eventually results in absolute insulin deficiency (1). Type 1 DM accounts for approximately ten percent of all DM cases. Type 2 DM is generally characterized by peripheral insulin resistance with relative insulin deficiency to predominant insulin secretory defeat with insulin resistance (1). Type 2 DM accounts for approximately ninety percent of all DM cases. The major risk factors in the development of type 2 DM are (3); Family history, Obesity, Race/ethnicity, Increasing age (especially greater than forty five years), Previous identified impaired fasting glucose or impaired glucose tolerance, Hypertension, Hyperlipidemia and History of gestational DM.

There is evidence that good glycaemic control can slow or prevent the development of diabetes complications (6-10). The Diabetes Control and Complication Trial (DCCT) demonstrated the association between the degree of glycaemic control and the development of microvascular complications in type 1 DM patients (11-12). The DCCT determined that there was an approximately 50% reductions in microvascular complications in the intensive treatment group and a non-significant tendency to fewer major cardiovascular events. Intensive control was accompanied by a significantly between the groups. The DCCT investigators did advice caution in extending the findings to patients with type 2 DM without careful regard for age and coexisting diseases. The United Kingdom Prospective Diabetes Study (UKPDS) was the largest scale long-term intervention study in newly diagnosed type 2 DM patients and involved over 5000 patients. The UKPDS used an intensive blood glucose control policy, which achieved a medium HbA1c of 7% compared with 7.9% in those randomized to conventional treatment over a median 10 years follow-up (9). The UKPDS confirmed the benefit of intense glycaemic control on microvascular disease in type 2 DM patients (4, 8-10, 13-20). The aim of the study to evaluate the patient clinical characteristics and risk factors for long term complications in the endocrine clinic of Hospital Penang, Malaysia.

Methods

Study design

This study aimed to describe the risk factors and association among sociodemographics, hence Descriptive Prospective cross-sectional study design was chosen. Managing diabetes is a lifelong process and requires total commitment from individuals with diabetes. Hence the framework of this study was based on the principle of eight risk factors (RF). RF1-Diabetes, RF2- Hypertension, RF3- Hyperlipidemia, RF4- Smoking, RF5-Male > 45years, RF6=Female > 55years, RF7- Hypoglycemia, RF8- No exercise (3x/week > 20min). RF1-Diabetes, since all the patients are from endocrine clinic so the rational effect of this variable is 100%.

Setting

As 70% of people with diabetes in Malaysia receive treatment in the government healthcare system, (21) data was collected from government healthcare settings. The general hospital is the main government hospital in the Penang state and is situated within the city area offering tertiary care. Subjects were not recruited from private clinics and hospitals due to problems with accessibility and differences in socioeconomic status which could bias the outcomes.

Sample Size

The required sample size was calculated with power analysis using the procedure provided by the Polit and Hungler (22). The power was set at 0.80 with alpha being set at 0.05. Since the value of the effect size (Gamma), was unavailable from previous similar studies and the pilot study sample size was small (19 subjects), the investigator chose to use the conversion based on the effect size convention table in Polit and Hungler (22). Polit and Hungler (22) advise to use medium effect size ranging from 0.2-0.3 for nursing studies. This provided a range of sample size from 88-197 subjects. For logistical reasons the study had to be a manageable size within the period of study, so the investigator chose the sample size using the medium effect size of Gamma y = 0.25. To achieve a power of 0.7 with alpha set at 0.05, 186 subjects were required for the study but researcher increase the sample to 297 in case of drop out.

Inclusion criteria. Subjects who met the following criteria were recruited: non-pregnant adults with either Type1 or Type 2 diabetes regardless of gender and ethnicity, 18 years and above (legal age for consent), diagnosed with diabetes with year of more, speaking and understanding either English, Bahasa Malaysia, Mandarin, Chinese dialects (Cantonese, Hokkien, Teow-chew) because these were the languages used during the interview, having poor diabetes control during the last one year. Even though glycated haemoglobin (HbA1c) is the gold standard for glycaemic assessment, it was not consistently measured for all diabetic patients in the healthcare system where the study was done. Therefore for the purpose of this study, poor diabetes control was defined as the mean of minimum of three fasting blood glucose (FBG) readings of more than 7 mmol/L in the last year. Prior studies have shown that FBG of more than 7 mmol/L is associated with increased micro-and macro-vascular complications (23-26).
Exclusion criteria. The following subjects were excluded: Were adults 18 years of age and more with either Type 1 of Type 2 diabetes unable to answer the questionnaires independently, such as having unstable medical condition, mental illness, and senility or hearing impairment. This was to avoid assistance from family members to cares that could introduce bias in the data collection; had poor vision and unable to assess visually the portion sizes of their carbohydrate food intake during dietary assessment; were women who were pregnant or had gestational diabetes due to different criteria on standard of control; had record of random blood glucose only because the definition of poor control was based on fasting blood glucose readings.

Research Tool
Self-developed data collection form was used to collect the patient information.

Ethical issues
The Research Ethics Committee of hospital and the Malaysian Medical Research and Ethics Committee approved the study. Written consents which included information to access the subjects' medical records were taken from all participants before the interviews. For those who were illiterate and not able to give their signature, thumbprints were used instead. The medical records were sourced for two pieces of information. First, the subjects' glycaemic status was attained namely fasting blood glucose levels to assist the investigator in identifying the potential subjects (inclusion criteria). Second, the subjects' current medication(s) were attained since research question three sorts to identify any relationship between medication concordance and poor glycaemic control. No other data was extracted from the medical records. Viewing and extracting information from the subjects' medical records was done solely by the investigator either at the medical in-patient wards or the medical outpatient clinics during official working hours.

Data Collection Procedure
Identification of Subjects. This was done initially by identifying all diabetic subjects. In the out-patient department of the hospital, the investigator worked closely with the nursing staff to identify patients with blood glucose tests done prior to doctors' consultation. They were familiar with their patients with poor glycaemic control or the nurse in-charge identified them via the patients' blood glucose results.
Places of Data Collection. Data collection was done in out-patient departments at the doctors' consultation rooms.

Statistical Analysis
The analysis was done in both descriptive and inferential statistics to make information in presentable form. Data is presented in both graphical and tabular forms. The Statistical package for Social Sciences (SPSS) version 19 ® was used for this analysis. The level of significance was set at 0.05 for all analysis.

Results

A total of 297 (100%) patients were enrolled from OPD diabetic clinic of Hospital Palau Pinang. Among the sample 150 (50.5%) were

TABLE 1. Frequency among gender of study population

Gender	F (%)	Age mean (±S.D.)
Male	150 (50.5)	58.23 (10.771)
Female	147 (49.5)	59.04 (10.414)
Total	297 (100.0)	58.64 (10.581)

TABLE 2. Mean age gender distribution among ethnic

Gender	Ethnic	Mean	N (%)	Std. Deviation
Male	Malay	53.20	40 (26.7)	12.831
	Chinese	62.10	77 (51.3)	8.612
	Indian	55.03	33 (22)	9.600
	Total	58.23	150 (50.5)	10.771
Female	Malay	54.03	36 (24.49)	8.013
	Chinese	63.43	81 (55.10)	11.090
	Indian	58.30	30 (20.41)	9.063
	Total	59.04	147 (49.5)	10.414
Total	Malay	53.61	76 (25.59)	10.627
	Chinese	62.75	158 (53.20)	9.959
	Indian	56.53	63 (21.21)	9.422
	Total	58.64	297 (100.0)	10.581

TABLE 3. Mean weight in kg at diagnosis gender distribution among ethnic

Gender	Ethnic	Mean	N (%)	Std. Deviation
Male	Malay	79.17	40 (26.67)	18.936
	Chinese	66.64	77 (51.33)	13.003
	Indian	69.19	33 (22)	11.314
	Total	70.34	150 (50.5)	15.185
Female	Malay	69.38	36 (24.49)	14.896
	Chinese	60.53	81 (55.10)	12.766
	Indian	59.95	30 (20.41)	11.069
	Total	62.37	147 (49.5)	13.382
Total	Malay	74.74	76 (25.59)	17.761
	Chinese	63.31	158 (53.20)	13.184
	Indian	64.96	63 (21.21)	12.019
	Total	66.29	297 (100.0)	14.815

TABLE 4. Characteristic determination of RF2 –hypertension during study duration

Characteristic	RF2-hypertension		Total N (%)	*p*-value
	Yes N (%)	No N (%)		
Gender				
Male	88 (58.7)	62 (41.3)	150 (100.0)	0.417
Female	93 (63.2)	54 (36.8)	147 (100.0)	
Ethnic				
Malay	44 (57.9)	32 (42.1)	76 (100.0)	
Chinese	102 (65.4)	54 (34.6)	156 (100.0)	0.296*
Indian	36 (55.4)	29 (44.6)	65 (100.0)	
Diagnosis				
IDDM	3 (100.0)	-	3 (100.0)	
Diabetes	8 (9.0)	81 (91.0)	89 (100.0)	0.000*
Diabetes and HPT	101 (100.0)	-	101 (100.0)	
Diabetes and other complication	69 (66.3)	35 (33.7)	104 (100.0)	
Medication consideration				
Insulin	3 (50.0)	3 (50.0)	6 (100.0)	
Insulin and oral	1 6 (66.7)	8 (33.3)	24 (100.0)	0.013*
BIDS	4 (22.2)	14 (77.8)	18 (100.0)	
Oral	156 (63.4)	90 (36.6)	246 (100.0)	
Diet and exercise	2 (66.7)	1 (33.3)	3 (100.0)	

Chi-square (*Pearson)

males and rest 147 (49.5%) females. Mean age distribution among gender is presented in Table 1. Ethnic distribution among males showed predominance of Chinese with 77 (51.3%) followed by Malays 40 (26.7%) and rest 33 (22%) were Indians. While among females almost same pattern was found. The mean ± S.D age differences were found

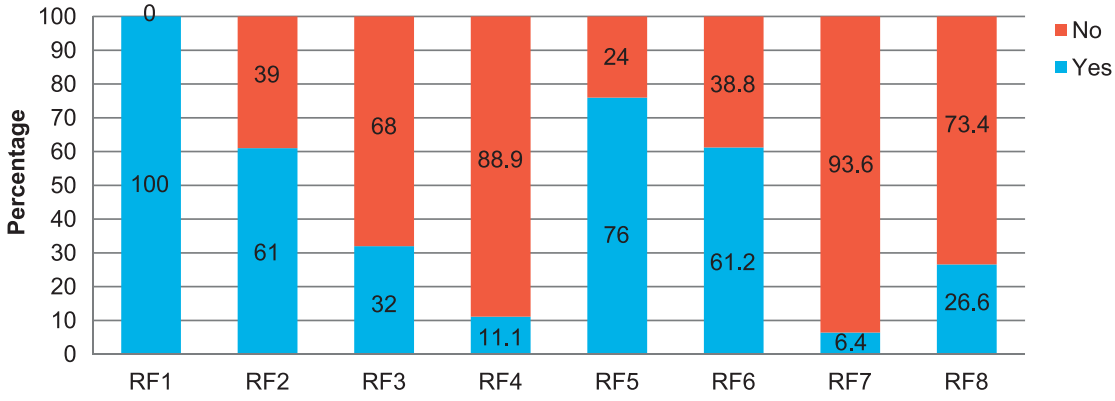

FIGURE 1. Clinical risk factors founds among enrolled patients. (RF1 = Diabetes, RF2 = Hypertension, RF3 = Hyperlipidemia, RF4 = Smoking, RF5 = Male >45years, RF6=Female>55years, RF7 = Hypoglycemia, RF8 = No exercise (3x/week>20min)).

TABLE 5. Characteristic determination of RF3 - hyperlipidemia in study population

Characteristic	RF3-hyperlipidemia		Total N (%)	*p*-value
	Yes N (%)	No N (%)		
Gender				
Male	43 (28.7)	107 (71.3)	150 (100.0)	0.0215
Female	52 (35.4)	95 (64.6)	147 (100.0)	
Ethnic				
Malay	20 (26.3)	56 (73.7)	76 (100.0)	
Chinese	55 (35.2)	101 (64.8)	156 (100.0)	0.258
Indian	20 (30.8)	45 (69 .2)	65 (100.0)	
Diagnosis				
IDDM	1 (33.3)	2 (66.7)	3 (100.0)	
Diabetes	2 (2.2)	87 (97.8)	89 (100.0)	0.000*
Diabetes and HPT	4 (4.0)	97 (96.0)	101 (100.0)	
Diabetes and other complication	88 (84.6)	16 (15.4)	104 (100.0)	
Medication consideration				
Insulin	3 (50.0)	3 (50.0)	6 (100.0)	
Insulin and oral	6 (25.0)	18 (75.0)	24 (100.0)	
BIDS	3 (16.7)	15 (83.3)	18 (100.0)	0.274*
Oral	83 (33.7)	163 (66.3)	246 (100.0)	
Diet and exercise	-	3 (100.0)	3 (100.0)	

Chi-square (*Pearson)

TABLE 6. Characteristic determination of RF4-Smoking in study population

Characteristic	RF4-Smoking		Total N (%)	*p*-value
	Yes N (%)	No N (%)		
Gender				
Male	28 (18.7)	122 (81.3)	150 (100.0)	0.000
Female	4 (2.7)	143 (97.3)	147 (100.0)	
Ethnic				
Malay	6 (8.0)	70 (92.0)	76 (100.0)	
Chinese	13 (8.3)	143 (91.7)	156 (100.0)	0.441*
Indian	12 (18.5)	53 (81.5)	65 (100.0)	
Diagnosis				
IDDM	1 (33.3)	2 (66.7)	3 (100.0)	
Diabetes	8 (9.0)	81 (91.0)	89 (100.0)	0.096*
Diabetes and HPT	8 (7.9)	93 (92.1)	101 (100.0)	
Diabetes and other complication	13 (12.5)	91 (87.5)	104 (100.0)	
Medication consideration				
Insulin	1 (16.7)	5 (83.3)	6 (100.0)	
Insulin and oral	3 (12.5)	21 (87.5)	24 (100.0)	0.552*
BIDS	1 (5.5)	17 (94.5)	18 (100.0)	
Oral	20 (8.1)	226 (91.9)	246 (100.0)	
Diet and exercise	-	3 (100.0)	3 (100.0)	

Chi-square (*Fisher exact)

variable among the three ethnics. Table 2 showed the distribution pattern of mean ± S.D of age among genders and also among the study population. Mean age comparison among genders showed females have high mean age (59.04 years) as compared to males (58.23 years). While comparing mean age difference among ethnics revealed Chinese mean age is 62.75 years followed by Indians with 56.53 years and least age to disease response among Malays 53.61 years. Mean weight of the study population was 66.29kg but upon analysis among genders it is found that males mean ± S.D (70.34 ± 15.185) is extensively higher as compared to females (62.37 ± 13.382). Further analysis by cross tabulation showed Malay males mean weight at the time of diagnosis significantly higher (p<0.001, one way ANOVA) as compared to other ethnics, same results found among Malay females (p<0.001, one way ANOVA). Table 3 showed cross-tabulation of mean weight distribution among gender and ethnics at the time of diagnosis. At the time of diagnosis body mass index (BMI) has been collected and results showed the mean BMI of the study population was 25.39 (297, 100%), among them females have higher BMI 25.79 as compared to males 24.97 at the time of diagnosis. The Figure 1 presents the percentage distribution of clinical risk factors among study population. Clinical risk factors are the individual parameters that might lead to increase long-term complications or co morbidities. More the clinical risk factors among the study population, it will give increase possibility to get higher complications. Findings suggested increased number of risk factors among the study population. Finding also showed that hypertension found among all the classes of diagnosis. Significant variable are diagnosis class and medication consideration. Table 4 provides the descriptive information about the RF-2 hypertension during the study duration among selected patients. Risk factor analysis results showed that hyperlipidemia have significant association among gender. Further analysis revealed that about 95 (32%) of our study population carrying this risk factor and majority of them 83 (87.4%) on the oral medication. Table 5 presented the finding of the analysis. Similarly smoking findings are presented in Table 6. Age above then 45 years for male and >55 years

TABLE 7. Characteristic determination of RF5-Male>45 years (N=114/150) among male in study population

Characteristic	N (%)	*p*-value
Ethnic		
Malay	27 (23.7)	
Chinese	65 (57.0)	0.000
Indian	22 (19.3)	
Diagnosis		
IDDM	1 (0.9)	
Diabetes	27 (23.7)	0.000
Diabetes and HPT	43 (37.7)	
Diabetes and other complication	43 (37.7)	
Medication consideration		
Insulin	1 (0.9)	
Insulin and oral	12 (10.5)	0.000
BIDS	5 (4.4)	
Oral	94 (82.5)	
Diet and exercise	2 (1.7)	

TABLE 8. Characteristic determination of RF6-Female > 55 years (N=90/147) among female in study population

Characteristic	N (%)	*p*-value
Ethnic		
Malay	16 (17.8)	0.000
Chinese	58 (64.4)	
Indian	16 (17.8)	
Diagnosis		
IDDM	1 (11.1)	
Diabetes	15 (16.7)	0.000
Diabetes and HPT	32 (35.5)	
Diabetes and other complication	42 (46.7)	
Medication consideration		
Insulin	3 (33.3)	
Insulin and oral	6 (6.7)	0.000
BIDS	1 (1.1)	
Oral	79 (87.8)	
Diet and exercise	1 (1.1)	

TABLE 9. Characteristic determination of RF7-Hypoglycaemia in study population

Characteristic	RF4-Hypoglycaemia		Total N(%)	*p*-value
	Yes N (%)	No N (%)		
Gender				
Male	14 (9.3)	136 (90.7)	150 (100.0)	0.457
Female	8 (5.4)	139 (94.6)	147 (100.0)	
Ethnic				
Malay	7 (9.2)	69 (90.8)	76 (100.0)	
Chinese	7 (4.5)	149 (95.5)	156 (100.0)	0.317
Indian	8 (12.3)	57 (87.7)	65 (100.0)	
Diagnosis				
IDDM	2 (66.7)	1 (33.3)	3 (100.0)	
Diabetes	9 (10.1)	80 (89.9)	89 (100.0)	0.016*
Diabetes and HPT	7 (6.9)	94 (93.1)	101 (100.0)	
Diabetes and other complication	4 (3.8)	100 (96.2)	104 (100.0)	
Medication consideration				
Insulin	2 (33.3)	4 (66.7)	6 (100.0)	
Insulin and oral	4 (16.7)	20 (83.3)	24 (100.0)	
BIDS	1 (5.6)	17 (94.4)	18 (100.0)	0.033*
Oral	13 (5.3)	233 (94.7)	246 (100.0)	
Diet and exercise	-	3 (100.0)	3 (100.0)	

Chi-square (*fisher exact)

TABLE 10. Characteristic determination of RF8-No Exercise (3x/week>20 min) in study population

Characteristic	RF8-No Exercise (3x/week>20 min)		Total N (%)	*p*-value
	Yes N (%)	No N (%)		
Gender				
Male	41 (27.3)	109 (72.7)	150 (100.0)	0.730
Female	38 (25.9)	109 (74.1)	147 (100.0)	
Ethnic				
Malay	21 (27.6)	55 (72.4)	76 (100.0)	
Chinese	38 (24.4)	118 (75.6)	156 (100.0)	0.032
Indian	18 (27.7)	47 (72.3)	65 (100.0)	
Diagnosis				
IDDM	-	3 (100.0)	3 (100.0)	
Diabetes	33 (37.1)	56 (62.9)	89 (100.0)	0.001*
Diabetes and HPT	18 (17.8)	83 (82.2)	101 (100.0)	
Diabetes and other complication	27 (26.0)	77 (74.0)	104 (100.0)	
Medication consideration				
Insulin	3 (50.0)	3 (50.0)	6 (100.0)	
Insulin and oral	4 (16.7)	20 (83.3)	24 (100.0)	
BIDS	4 (22.2)	14 (77.8)	18 (100.0)	0.037*
Oral	63 (25.6)	183 (74.4)	246 (100.0)	
Diet and exercise	-	3 (100.0)	3 (100.0)	

Chi-square (*fisher exact)

for females is important factor for complications and long-term medical problems. Upon analysis of this variable we find similar results of significant association with ethnic, diagnosis class and medication consideration. Results showed that 114 (76%) of our study males are > 45 years while 90 (61.2%) of females were > 55 years. Detailed descriptive data is presented in Table 7 & 8.

Hypoglycemic evidence has an association with diagnosis class and medication consideration, no significant differences has been found among gender and ethnicity of the study population (Table 9). Majority of the patients having no social habit of exercise, table 10 describes the relation and association of no-exercise risk factors with characteristic variables among study population.

Discussion

The World Health Organization projects that by the year 2025 more than 5% of the world population, i.e. 300 million people will suffer from diabetes. A patient who suffers from type 2 diabetes has a 2–4 times greater risk of death from cardiovascular causes than the patient without diabetes (27). The most Hypertension and Diabetes 83 common cause of dying in the diabetic patient is heart disease. In addition, peripheral vascular disease, end-stage renal disease, blindness and amputations are common co-morbidities in diabetic patients. Hypertension has been identified as a major risk factor for the development of diabetes. Patients with hypertension are at a 2–3 times higher risk of developing diabetes than patients with normal blood pressure (28). Hypertension by itself is, of course, a powerful risk factor for cardiovascular morbidity and mortality as established by data from the Framingham cohort more than three decades ago. For any given level of systolic blood pressure, the occurrence of diabetes distinctly increases cardiovascular mortality. Stamler et al. (29) have documented that diabetes in the normotensive patient confers greater risk than a systolic blood pressure between 160 and 170mm Hg. This observation provoked Haffner and Cassells' (30) observation that the prognosis of diabetes is just as grim as the one of a patient who has suffered an acute myocardial infarction. Of note, while this is true for overall cardiovascular mortality, it does not necessarily mean that diabetes and hypertension are synonymous in affecting the individual components of cardiovascular system. Also, it does by no means follow that specific cardiovasculardrugs are equally protective in diabetes and coronary artery disease. Blood pressure control remains unacceptably low in the general population, but is even lower in the diabetic hypertensive patient (31). Although controlling the blood pressure is a commendable goal of antihypertensive therapy, treating hypertensive cardiovascular disease in the diabetic patient is more complex than simply achieving blood pressure targets. Recent studies have shown that antihypertensive drug classes have differing effects on the risk of new onset diabetes, on metabolic endocrine surrogate endpoints and possibly on outcome (32).

Clinical finding in cardiovascular problems in Diabetes patients

Diabetes mellitus is associated with a high risk of cardiovascular disease and is the leading cause of end-stage renal disease, blindness, and non-traumatic amputations in western countries (33). Elevated but nondiabetic levels of fasting glucose also carry a higher risk of cardiovascular disease (34). As a cardiovascular risk factor, glycemia is a continuous variable with no sudden increase in risk (35). The extreme state is the metabolic syndrome that is associated with a 2- to 3-fold increase in cardiovascular morbidity and mortality (36-38). Hypertension by itself is a powerful risk factor for cardiovascular morbidity and mortality. Although the effects of diabetes mellitus and hypertension on the cardiovascular system vary somewhat and are often distinct, their combined presence in the same patient is destructive (39). The common denominator of hypertensive/ diabetic target organ disease is the vascular tree, which is affected by both disorders. *The Vascular Tree.* Both hypertension and diabetes are well-identified risk factors for atherogenesis. Several mechanisms acting together mediate the damage to the vascular tree in the diabetic hypertensive patient (39). Metabolic abnormalities that often present in diabetic hypertensive patients accelerate atherosclerosis. Plasma levels of lipoprotein have been noted to be elevated in diabetic individuals, particularly those with poor glycemic control. Augmented oxidation of low-density lipoprotein cholesterol and formation of glycated low-density lipoprotein, which enhance foam cell formation, have been observed in diabetic states. Anatomic and functional abnormalities of the vascular endothelium have been described in diabetes mellitus and hypertension (39). Hyperglycemia activates protein kinase C in endothelial cells, which may enhance vascular tone, per-

meability, and atherosclerosis. Elevated circulating levels of insulin as exist in type 2 diabetes and in many patients with essential hypertension may contribute either directly or in conjunction with insulin-like growth factor (IGF) to the accelerated atherosclerosis associated with these conditions. Insulin and IGF-1 may exert their atherogenic effects through influences on both vascular endothelial cells and vascular smooth muscle cells (39). Diabetes mellitus and hypertension are also associated with hematologic abnormalities that encourage thrombosis. Enhanced platelet adhesion and aggregation as well as higher than normal levels of some coagulation factors contribute to the procoagulation state in diabetic hypertensive patients (39). Diabetes seems to be a specific risk factor for small vessel disease. In contrast, hypertension, at least in its nonmalignant form, seems to affect predominantly the large arteries. Together, the two disorders synergistically damage the arterial tree. *Heart and Coronary Artery Disease.* Diabetes mellitus is associated with a markedly increased prevalence of coronary artery disease. The prevalence of coronary artery disease as assessed by various diagnostic methods is as high as 55% among adult patients with diabetes mellitus as compared to 2–4% of the general population (40). Moreover, the cardiovascular mortality rate is more than doubled in men and more than quadrupled in women who have diabetes mellitus compared to those without. The restenosis rate after coronary balloon angioplasty is about 2-fold higher in diabetic than nondiabetic patients (41). Due to autonomic neuropathy diabetic patients have a decreased perception of ischemic pain, which contributes to a high prevalence of silent ischemia (42). Diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction (43). Myocardial ischemia is common in patients with hypertension (44) and caused by several pathogenic mechanisms. (a) Hypertension accelerates arteriosclerosis of the coronary arteries. (b) Elevated blood pressure increases left ventricular wall stress, wall tension, and stroke work. (c) Resistance of the coronary microvasculature is abnormally elevated in hypertensive patients even in the absence of left ventricular hypertrophy. (d) Long-standing hypertension causes left ventricular hypertrophy that increases the diffusion distance, compromises the vasodilator reserve of the coronary circulation and increases the oxygen demand of the myocardium (27, 45). It should be noted that hypertensive patients, especially those with left ventricular hypertrophy, are as susceptible to silent myocardial ischemia as patients with diabetes (46). Coronary artery disease is much more common in diabetic hypertensive patients than in patients suffering from hypertension or diabetes alone (47). For all 2,681 men in the PROCAM trial who had none of the three risk factors (i.e. hypertension, diabetes, or hyperlipidemia), the coronary artery disease incidence was 6/1,000 in 4 years. In contrast, the incidence of coronary artery disease in those participants who were suffering from hypertension or diabetes was 14 and 15 per 1,000 in 4 years, respectively. When both risk factors were present in the same patient, the incidence rate increased to 48 per 1,000 (47). Diabetes, and to a lesser extent hypertension, may alter the perception of ischemic pain, leading to a high prevalence of silent ischemia. Melina et al. (35) found a high prevalence of asymptomatic ST segment depression in diabetic patients with essential hypertension. The number of ST segment depression episodes was significantly related to glycosylated hemoglobin levels, left ventricular mass, and ambulatory systolic and diastolic blood pressure variability and hypertensive peaks.

Hyperlipidemia

Lipoprotein Pattern in Diabetes. The most typical lipoprotein pattern in diabetes, also known as diabetic dyslipidemia or atherogenic dyslipidemia, consists of moderate elevation in triglyceride levels, low HDL cholesterol values, and small dense LDL particles. This lipoprotein pattern is associated with insulin rsistance and is present even before the onset of diabetes. LDL cholesterol levels in type 2 diabetic subjects are generally similar to those found in the general population. Small dense LDL particles are highly atherogenic because of their enhanced susceptibility to oxidative modification and increased uptake by the arterial wall. At triglyceride levels > 132 mg/dl, small LDL particles become common (49). Overall, 30–40% of patients with diabetes have triglyceride levels > 200 mg/dl, and 10% have triglycerides > 400 mg/

dl (50). However, in the U.K. Prospective Diabetes Study, despite a high frequency of modestly elevated baseline triglyceride levels (mean baseline 159 mg/dl), a multivariate analysis showed that triglyceride levels did not predict CHD events. LDL cholesterol was the strongest independent predictor of CHD followed by HDL cholesterol, (51) supporting current national guidelines in which LDL lowering is the primary lipid target.

Diabetes management

Improving glycemic control in individuals with moderate to severe hyperglycemia regardless of type of treatment is associated with improvement in lipid values. Among the available oral therapeutic options for type 2 diabetes, treatment with metformin and thiazolidinediones has been associated with beneficial effects on lipids. Metformin has been associated with modest reduction in triglyceride levels in hyperlipidemic and hypertensive patients (52). In a head-to-head comparison study, (53) pioglitazone was associated with significant triglyceride reduction, whereas there was no net triglyceride change with rosiglitazone. Although both agents increased HDL cholesterol and LDL cholesterol, pioglitazone was associated with a greater increase in HDL cholesterol and less LDL cholesterol increase than rosiglitazone.

Smoking

Smokers with Type 1 and Type 2 diabetes are at increased risk of illness and premature death, mostly through development of cardiovascular disease, but other disease processes associated with diabetes may also be made worse by smoking (54-55). Smokers with Type 1 diabetes in particular may have a higher risk of developing kidney disease, and possibly eye and nerve damage as well, whereas smokers with Type 2 diabetes are more likely to increase their risk of coronary heart disease, stroke and peripheral vascular disease (56). Evidence is also accumulating that shows that smoking is associated with an elevated risk of developing Type 2 diabetes (57-62). A major review and meta-analysis of published data has found that current smokers are more likely to develop diabetes than ex-smokers and never smokers, and that smokers of 20 or more cigarettes a day are at greater risk than lighter smokers (63). Overall, current smokers are estimated to have a 44% greater risk, and ex-smokers a 23% greater risk of developing Type 2 diabetes than people who have never smoked (63). Plausible biological mechanisms for this association include increased insulin resistance, altered insulin secretion and other impairments to pancreatic function noted in smokers (63). According to the authors of this review, 'the relevant question should no longer be whether this association exists, but rather whether this established association is causal.'(63 p2660) If further research proves a causal relationship between smoking and Type 2 diabetes, it can be expected to have a major impact on future estimates of tobacco-caused morbidity and mortality in Australia and globally. Smokers experience a poorer level of overall general health than non-smokers (64). Taking into account possible confounding factors such as alcohol use, socioeconomic background, age and gender, smokers also report higher levels of tiredness or fatigue, reduced wellbeing and satisfaction with life, slightly lower self-reported measures of mental wellbeing, and increased incidence of psychological symptoms such as depressed mood and anxiety. In the elderly, smoking is associated with accelerated declines in physical function, and increased levels of clinical illness and physical and cognitive impairment (64). Smokers are also more likely to report a history of pain during health examinations (65). It is understood that the circulation throughout the body of toxic constituents of tobacco smoke causes a number of diseases of many organs, as detailed in the preceding sections. The widespread distribution of tobacco smoke components may also be responsible for a more general decrement in health, through altered inflammatory/immune processes, oxidative stress and subclinical organ injury (64). Smokers are also more likely to experience sleep disturbances, including taking longer to fall asleep, being less likely to stay asleep, and having less total sleep time than non-smokers (66-67).

Smoking and absence from work due to illness.

Smokers are more likely to miss work due to ill-health, have longer duration of absence from work, and access all levels of medical care more frequently. Work absences are reportedly higher in smokers resulting from a broad range of symptoms,

including problems with the digestive tract, neck, back and upper limbs. These effects are evident in younger smokers, before the effects of major tobacco-caused disease become apparent during middle age and later years.5 There is also substantial evidence that smokers are more likely to suffer injury in the workplace than non-smokers (64). Australian data show that men who smoke are 66% more likely to be absent from work than male never-smokers, and that female smokers are 23% more likely to miss work than female never-smokers (68). This in turn has a major quantifiable economic impact on the nation's productivity (69).

Hypoglycaemia

Low blood sugar, also called hypoglycemia, is a condition that occurs when the amount of sugar in a patient's blood is lower than normal. Blood sugar levels less than 70 mg/dL are considered to be dangerously low and may cause damage to the patient's tissues, reports MedlinePlus, a National Institutes of Health website (70). Hypoglycemia can cause a variety of long-term effects or complications.

Deficiencies in Neurodevelopment

Newborn babies, or neonates, who suffer from recurrent episodes of low blood sugar levels can develop deficiencies in neurodevelopment, states an article in the April 1999 issue of the Journal of Pediatrics (72). Neurodevelopment pertains to the growth and maturation of the brain and other aspects of the nervous system. Neonates, especially premature babies, who have been affected by hypoglycemia, may have reduced head circumferences and score lower on psychometric tests. These effects can last up to five years after birth. Even mild to moderate cases of hypoglycemia in neonates should be treated promptly to avoid these long-term complications.

Coma

Coma, or chronic loss of consciousness, may be a long-term effect of hypoglycemia, according to MedlinePlus (70). Hypoglycemia that results in coma is commonly called insulin shock. Without adequate levels of blood sugar, the brain is unable to obtain enough energy to function. Decreased brain function over a long period of time typically results in coma. Patients in a coma are unresponsive to external stimuli and may need assistance breathing and ingesting nutrients. Comas may last between a few hours to several months. Treating the hypoglycemic disorder usually brings the patient back to a conscious state (71).

Death

Without sugar, or glucose, the body is unable to function. Glucose provides much of the energy the body needs to survive. As blood sugar levels fall, multiple organs, especially the brain, begin to fail, warns MayoClinic (71). If left untreated, this condition may lead to death. Patients must recognize the early signs of hypoglycemia in order to avoid this dreaded outcome (72).

Physical Activity

The possible benefits of physical activity for the patient with type 2 diabetes are substantial, and recent studies strengthen the importance of long-term physical activity programs for the treatment and prevention of this common metabolic abnormality and its complications. Specific metabolic effects can be highlighted as follows (73). Glycemic control several long-term studies have demonstrated a consistent beneficial effect of regular physical activity training on carbohydrate metabolism and insulin sensitivity, which can be maintained for at least 5 years (74-75). These studies used physical activity regimens at an intensity of 50–80% *V*o2max three to four times a week for 30–60 min a session (74). Improvements in HbA1c were generally 10–20% of baseline and were most marked in patients with mild type 2 diabetes and in those who are likely to be the most insulin resistant (76). It remains true, unfortunately, that most of these studies suffer from inadequate randomization and controls, and are confounded by associated lifestyle changes (77). Data on the effects of resistance exercise are not available for type 2 diabetes although early results in normal individuals and patients with type 1 disease suggest a beneficial effect (73, 75). It now appears that long-term programs of regular physical activity are indeed feasible for patients with impaired glucose tolerance or uncomplicated type 2 diabetes with acceptable adherence rates (79). Those studies with the best adherence have used an initial period of su-

pervision, followed by relatively informal home physical activity programs with regular, frequent follow-up assessments (80). A number of such programs have demonstrated sustained relative improvements in *V*o2max over many years with little in the way of significant complications (81).

Exercise and Type 1 Diabetes

All levels of physical activity, including leisure activities, recreational sports, and competitive professional performance, can be performed by people with type 1 diabetes who do not have complications and are in good blood glucose control (note previous section) (76-78). The ability to adjust the therapeutic regimen (insulin and medical nutrition therapy) to allow safe participation and high performance has recently been recognized as an important management strategy in these individuals (77). In particular, the important role played by the patient in collecting self-monitored blood glucose data of the response to physical activity and then using these data to improve performance and enhance safety is now fully accepted (73-75). Hypoglycemia, which can occur during, immediately after, or many hours after physical activity, can be avoided. This requires that the patient has both an adequate knowledge of the metabolic and hormonal responses to physical activity and well-tuned self-management skills (76). The increasing use of intensive insulin therapy has provided patients with the flexibility to make appropriate insulin dose adjustments for various activities (79). The rigid recommendation to use carbohydrate supplementation, calculated from the planned intensity and duration of physical activity, without regard to glycemic level at the start of physical activity, the previously measured metabolic response to physical activity, and the patient's insulin therapy, is no longer appropriate. Such an approach not infrequently neutralizes the beneficial glycemic lowering effects of physical activity in patients with type 1 diabetes (80). General guidelines that may prove helpful in regulating the glycemic response to physical activity can be summarized as follows (73-76):

1. Metabolic control before physical activity - Avoid physical activity if fasting glucose levels are _250 mg/dl and ketosis is present, and use caution if glucose levels are _300 mg/dl and no ketosis is present. Ingest added carbohydrate if glucose levels are _100 mg/dl.
2. Blood glucose monitoring before and after physical activity - Identify when changes in insulin or food intake are necessary. Learn the glycemic response to different physical activity conditions.
3. Food intake - Consume added carbohydrate as needed to avoid hypoglycemia. Carbohydrate-based foods should be readily available during and after physical activity.

Because diabetes is associated with an increased risk of macrovascular disease, the benefit of physical activity in improving known risk factors for atherosclerosis is to be highly valued. This is particularly true in that physical activity can improve the lipoprotein profile, reduce blood pressure, and improve cardiovascular fitness (76). However, it must also be appreciated that several studies have failed to show an independent effect of physical activity training on improving glycemic control as measured by the A1C test in patients with type 1 diabetes. Indeed, these studies have been valuable in changing the focus for physical activity in diabetes from glucose control to that of an important life behavior with multiple benefits (76, 80). The challenge is to develop strategies that allow individuals with type 1 diabetes to participate in activities that are consistent with their lifestyle and culture in a safe and enjoyable manner (78). In general, the principles recommended for dealing with physical activity in adults with type 1 diabetes, free of complications, apply to children, with the caveat that children may be prone to greater variability in blood glucose levels. In children, particular attention needs to be paid to balancing glycemic control with the normalcy of play, and for this the assistance of parents, teachers, and athletic coaches may be necessary. In the case of adolescents, hormonal changes can contribute to the difficulty in controlling blood glucose levels (3,54, 70). Despite these added problems, it is clear that with careful instructions in self-management and the treatment of hypoglycemia, physical activity can be a safe and rewarding experience for the great majority of children and adolescents with type 1 diabetes (15, 27, 31, 54, 72).

Exercise in the Elderly

Evidence has accumulated suggesting that the progressive decrease in fitness and muscle mass and strength with aging is in part preventable by maintaining regular physical activity (81). The decrease in insulin sensitivity with aging is also partly due to a lack of physical activity. Lower levels of physical activity are especially likely in the population at risk for type 2 diabetes (1, 81). A number of recent studies of exercise training have included significant numbers of older patients (49, 78). These patients have done well with good training and metabolic responses, levels of adherence at least as good as the general population, and an acceptable incidence of complications (49). It is likely that maintaining better levels of fitness in this population will lead to less chronic vascular disease and an improved quality of life (57).

Conclusion

Majority of patients are at high risk of long-term complications and comorbidies. It has been found that increased rate of risk factors have been found among the study population and non-significant to sociodemographic differences.

Competing interests

The authors declare no conflicts of interest.

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