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Evaluating the effect of glycaemic control, blood pressure, lipid profile and diabetes duration on developing diabetes complications and its progression

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Abstract

Purpose: This study was aimed to evaluate the effect of glycaemic control, blood pressure, lipid profile and diabetes duration on developing diabetes complications and its progression. Methods: One thousand and fourteen patients attending outpatient diabetes clinic at a hospital in the northern part of Malaysia were retrospectively followed. Data were collected over a period of three years. Data were analysed using SPSS software package version 15.0 (SPSS Inc., Chicago, IL, U.S.A.). Results: Diabetes was more predominant among the Chinese and female patients. Hypertension and dyslipidaemia concurrently was found among 43% of the patients as comorbidity. The majority of the participants didn't achieve good glycaemic control (92.9%). Patients with two complications had the highest HbA1c level (8.5 ± 2%) (P=0.035). There were no significant differences in the BP and lipid profile between the groups in relation to the number of complications (P>0.05). As the disease duration increases there were a decrease in the number of patients with no complications and an increment in the number of patients with a number of complications. Conclusions: There were significant differences in glycaemic control in relation to the diabetic complications in addition to the obvious differences in the number of complications and comorbidities occurrence as the disease progressed.

Keywords: Diabetes mellitus, Glycaemic control, lipid profile, blood pressure, complications, comorbidities, disease duration.

INTRODUCTION

Diabetes mellitus (DM) is becoming a worldwide epidemic. It is recognized as one of the most common non-communicable diseases and a major cause of mortality and morbidity in Malaysia and globally[1-3]. There will be three-fold increase of this disease in Asia, both in developed countries like China and India, and in the rapidly developing countries such as Malaysia and Singapore[3]. In the last two decades, Malaysia has undergone a rapid growth, including an improved quality of life, a reduced mortality rate, and an increased life expectancy among the population. Unfortunately, this great progress also makes Malaysia highly prone to the diabetes epidemic[4]. In order to properly manage the disease, patients with diabetes must comply with both dietary and pharmacologic therapy. Understanding this disease and its complications will help to promote compliance. Given that each anti-diabetic agent can lower HbA1c level to some extent, we must determine the best ways to optimize their effects in treating diabetes. Furthermore, given the chronic and costly nature of diabetes, it is important to know the best treatment strategies that lead to the best glycaemic control, i.e., the most dramatic reduction in HbA1c. This will prevent or reduce the incidence of macro vascular and micro vascular complications, thereby decreasing the burden on both the patients and the healthcare sector[5]. The proportion of the diabetic patients who can achieve the target glycaemic control is varied from a population to another. This depends on many factors; the treatment and the patients' compliance to the treatment are part of these factors. In Malaysia, there is a high proportion of uncontrolled diabetes despite taking anti-diabetic therapy by the patients[6,7]. Two studies conducted elsewhere (Japan and the U.S) have 3 reported that the percentage of patients with good glycaemic control were more than the percentage of patients with poor glycaemic control[8,9]. To our knowledge, there was no study in Malaysia that investigated patient's glycaemic control, blood pressure, lipid profile and diabetes duration on developing diabetes complications and comorbidities. This study aimed to determine these.

MATERIALS AND METHODS

This was a cross-sectional study involving patients with diabetes type 2[10]; who attended outpatient diabetes clinic at a hospital in the northern part of Peninsular Malaysia. Patients' clinical data were observed and evaluated retrospectively for three years (from 2005 until 2007). Data were collected between February and July 2008. Patients were conveniently selected from outpatient's department of the hospital according to eligibility criteria of the study. Study eligibility criteria included: patients having type 2 DM, aged 21 years and above, receiving treatment for their diabetes. The excluded patients from this study: those with type 1 DM, on diet therapy only, and patients whose HbA1c and fasting plasma glucose (FPG) were not monitored regularly during the 3-year retrospective review.

Sample size and sampling method

The sample size needed for the study was calculated using the equation below [11-13]:

$$n = \frac{z^2\, p(1-p)}{d^2}$$

Where n = the sample size; Z = the statistic for the 99% level of confidence used in the power analyses, which was 2.58; p = the expected prevalence or the proportion used, which was 0.5; and d = the precision used, which was 0.05. The minimum sample size estimated for the study was 666 patients. The study enrolled 1014 patients who were attending the clinic during the study period. This increment in the sample size was to decrease possibility of incomplete data making it more predictive and more power of precision.

Data Collection Form and the Collection Procedure

A standardized data collection form was designed for use in the research. First step was obtaining approval from ethics committee Clinical Research Centre at Penang General Hospital to conduct this study. Data were collected retrospectively by reviewing past medical records of the study population over a 3-year period.

Outcome Measures reference

Glycaemic control and lipid profile target values presented are in accordance to the hospital's normal laboratory values. Blood pressure target values presented in accordance with the Malaysian Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus, Third Edition, 2004.

Data Analyses

The collected data were stored and analysed by using SPSS software package version 15.0 (SPSS Inc., Chicago, IL). Both descriptive and inferential statistics were applied wherever

necessary. Meanwhile, the primary and secondary outcomes of the study were calculated as the mean ± SD, since they are continuous variables. In addition, primary, secondary outcomes of the study were categorised according to the hospital laboratory values and Malaysian guidelines, respectively to determine the proportion of patients who achieved the target values. To examine data distribution and to ensure its normality, histogram bar was used. Histogram bar showed that TG value was not normally distributed. Therefore, a non-parametric test was applied for the triglyceride value only. One Way ANOVA test was applied to investigate the statistical differences between complications, and comorbidities in term of the FPG, HbA1c, blood pressure and lipid profile (except for the triglyceride level, which was analysed using the Kruskal-Wallis test). Moreover, number of complications, and type of co-morbidities was cross-tabulated against the disease duration to determine the association between them using the Chi-Square (χ^2) test. The statistical significance was defined as p value ≤ 0.05.

RESULTS AND DISCUSSION

One thousand and fourteen outpatients with type 2 diabetes were enrolled in the study and all of them were included in the analysis[10]. All the enrolled patients had FPG measurements through the evaluation period, while only 81.9% (n = 830) had HbA1c measurements throughout the retrospective period of review[10]. Mean weight (± SD) of the study participants was 65.62 ± 12.96 Kg; female patients constituted 54% and more than half of the study population were Chinese (54.1%) and the rest were Malay and Indian ethnic. Two thirds of participants had diabetes mellitus during the last 10 years, and 43% of them had two comorbidities (hypertension and dyslipidemia)[10]

From Table 1 we can see the majority of the participants didn't achieved good glycaemic control [10]. However about more than one third of them could achieve good blood pressure[10]. Furthermore, about half of the participants have a good control on their LDL and total cholesterol. In addition, one third of them could achieve a desirable TG level.

Table 2 shows patients with hypertension and dyslipidaemia concurrently had the highest HbA1c ($p = 0.015$). It is obvious that patients with hypertension had the lowest LDL cholesterol level, while patients with dyslipidaemia had the highest LDL cholesterol level. There were statistically significant differences in the triglyceride level between the groups defined by the co-morbidities. Also patients with hypertension had the lowest total cholesterol level, and patients with dyslipidaemia had the highest total cholesterol level ($p < 0.001$). There were significant differences in the systolic BP between groups of patients with co-morbidities. Patients with dyslipidaemia had the lowest systolic BP.

Table 1: Proportion of diabetic patients who achieved target values for plasma glucose blood pressure and lipid profile at Penang General Hospital (2005-2007)

Outcomes	Number of patients	Percentage
FPG (mmol/l)		
3.5– 6.7	272	26.8
>6.7	742	73.2
Total	1014	100
HbA1c (%)		
4 - 6	59	7.1
>6	771	92.9
Total	830	100
Target BP for patients with normal renal function (SBP/DBP)		
≤ 130/80 mmHg	339/465	33.4/45.9
>130/80 mmHg	675/549	66.6/54.1
Total	1014	100
HDL (mmol/l)		
<1; major risk factor CHD	112	11.1
>1; negative risk factor CHD	897	88.9
Total	1009	100
LDL (mmol/l)		
<3.3; low risk CHD	493	49.3
3.3 – 4.9	484	48.4
>4.9; high risk CHD	22	2.2
Total	999	99.9
TG (mmol/l)		
<1.7; desirable	304	30
1.7 – 2.3; border line	485	47.9
>2.3; high risk CHD	223	22
Total	1012	99.9
Total Cholesterol (mmol/l)		
<5.2; desirable	453	44.7
5.2 – 6.2; boarder line	399	39.4
>6.2; high risk CHD	161	15.9
Total	1013	100

FPG = fasting plasma glucose; HbA1c = haemoglobin A1c; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; TG = triglycerides.

Table 2: Patient's comorbidities in relation to their plasma glucose, blood pressure and lipid profile at Penang General Hospital (2005-2007)

Outcome measure	No. of patients	Hyper.	Dys.	Hyper+Dys.	No comorbidity	*p*- value*
HbA1c (%)	830	7.8 ± 1.6	8.2 ± 2	8.3 ± 1.8	7.9 ± 1.6	0.015
HDLmmol/l±SD	1009	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.205
LDLmmol/l±SD	999	2.9 ± 0.7	3.6 ± 0.7	3.4 ± 0.8	3.1 ± 0.6	< 0.001
Median of TG (IQR)	-	1.5 (0.8)	1.8 (1)	1.9 (1.1)	1.5 (0.7)	<0.001
Total choles. mmol/l±SD	1013	4.9 ± 0.8	5.7 ± 0.8	5.6 ± 1	5.1 ± 0.7	< 0.001
SBP(mmHg±SD)	1014	137.1±8.6	132.2± 9	137.2 ± 8.1	133 ± 9.2	< 0.001
DBP(mmHg±SD)	1014	82.8 ± 5	80.8±5.4	82.3 ± 4.7	80.5 ± 5.1	< 0.001

Table 3: Patient's number of complications in relation to their plasma glucose, blood pressure and lipid profile at Penang General Hospital (2005-2007)

Outcome measure	No. of patients	No. of comp.	1 comp.	2 comp.	3 comp.	4 comp.	5 comp.	*p*- value*
HbA1c (%)	830	7.9 ± 1.6	8.1 ± 1.8	8.5 ± 2	8.1 ± 1.7	7.9 ± 1.9	8.3 ± 1.9	0.035
HDLmmol/l±SD	1009	1.3 ± 0.34	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.4	0.885
LDLmmol/l±SD	999	3.3 ± 0.8	3.3 ± 0.8	3.3 ± 0.9	3.2 ± 0.7	3.3 ± 0.9	3.6 ± 1.1	0.743
Median of TG (IQR)	-	1.7 (1)	1.7 (0.9)	1.7 (1)	1.5 (0.6)	1.8 (1)	1.7 (1.2)	0.096
Total choles. mmol/l±SD	1013	5.4 ± 0.9	5.4 ± 0.9	5.5 ± 1.2	5.2 ± 0.7	5.4 ± 1.1	5.7 ± 1.1	0.509
SBP(mmHg±SD)	1014	135.6 ± 8.5	135.1 ± 8.8	135.9 ± 9.4	134.5 ± 8.8	137.8 ± 9	135.6 ± 8	0.696
DBP(mmHg±SD)	1014	82.1 ± 5.2	81.8 ± 5	81.1 ± 4.6	82.1 ± 5.7	83.6 ± 5.8	81.7 ± 5.8	0.174

Table 4: The association of diabetes duration in relation to the number of complications and comorbidities.

	Disease duration (years)							
	1-5	**6-10**	**11-15**	**16-20**	**21-25**	**26-30**	**Total**	**p-value***
Complication								<0.0001
No complication	158 (38.2)	134 (32.4)	66 (16)	38 (9.2)	6 (1.5)	11 (2.7)	413 (100)	
1 complication	119 (37.2)	91 (28.4)	61 (19.1)	31 (9.7)	10 (3.1)	8 (2.5)	320 (100)	
2 complications	55 (27.8)	51 (25.8)	41 (20.7)	29 (14.6)	12 (6)	10 (5.1)	198 (100)	
3 complications	18 (31.6)	14 (24.6)	8 (14)	10 (17.5)	3 (5.3)	4 (7)	57 (100)	
4 complications	4 (26.7)	4 (26.7)	2 (13.3)	4 (26.7)	1 (6.6)	0 (0)	15 (100)	
5 complications	4 (36.3)	2 (18.2)	2 (18.2)	1 (9.1)	1 (9.1)	1 (9.1)	11 (100)	
Total	358 (35.3)	296 (29.2)	180 (17.8)	113 (11.1)	33 (3.2)	34 (3.4)	1014 (100)	
Comorbidity								0.001
Hypertension	56 (25.9)	61 (28.2)	44 (20.4)	33 (15.3)	12 (5.6)	10 (4.6)	216 (100)	
Dyslipidemia	88 (41.7)	63 (29.9)	37 (17.5)	14 (6.6)	4 (1.9)	5 (2.4)	211 (100)	
Hypertension+dyslipidemia	146 (33.5)	127 (29.1)	79 (18.1)	54 (12.4)	12 (2.8)	18 (4.1)	436 (100)	
No comorbidity	68 (45)	45 (29.8)	20 (13.2)	12 (7.9)	5 (3.3)	1 (0.7)	151 (99.9)	
Total	358 (35.3)	296 (29.2)	180 (17.7)	113 (11.1)	33 (3.3)	34 (3.4)	1014 (100)	

*Chi- Square test . $P < 0.05$ is considered statistically significant

Table 3 shows that there were significant differences between groups based on number of the complications in terms of the HbA1c level: patients with two complications had the highest HbA1c level (8.5 ± 2%). There were no significant differences in the systolic or diastolic BP, HDL cholesterol level, LDL cholesterol level, triglyceride level and the total cholesterol level between the groups based on complications.

Table 4 shows that as the disease duration decrease patients with less complications increase as well as patients with no complications. Similarly, for the comorbidities occurrence as the disease duration increase patients with hypertension and dyslipidimea increase and conversely patients with no comorbidity decrease.

More than half of the diabetic patients in our study were female, the high proportion of females with diabetes may relate to many factors like high BMI (females had high BMI than male), physical inactivity, their sex hormones, and previous GDM [14]. The diabetic population was predominantly Chinese in ethnicity; the high incidence of diabetes among the Chinese in Penang may be due to its large Chinese population. Concurrent hypertension and dyslipidaemia were noted in the majority of this study population. Similar results have been demonstrated by Rodondi and colleagues (2006) who reported that about half of their study population had hypertension and dyslipidaemia concurrent with diabetes. Furthermore, three studies reported that the majority of diabetic patients had concurrent hypertension with the diabetes [15-17]. The high incidence of co-morbidities in the current study may relate to the diabetic patients' noncompliance in taking medications, as well as possible deficit in knowledge about the nature of the disease and its complications. However, differences in lifestyle, exercise, type of diet, and geographic location may also be contributory. All of the diabetic patients who were included in this study were receiving anti-diabetic therapy; however, the majority of them did not achieve optimum glycaemic control (HbA1c 4-6%; FPG 3.5-6.7 mmol/l). In Malaysia, poor glycaemic control was illustrated in six studies. Tan and colleagues (2008) at Sarawak General Hospital showed that only 26% of their diabetic patients achieved an HbA1c level of less than 7%. Meanwhile, Mafauzy showed that up to 41% of the diabetic population had an HbA1c level of less than 7% [18], while only 18% of the diabetic population had an FPG level of less than 6.1 mmol/l [18]. Ismail *et al.* (2000) have shown that a high percentage (61.1%) of the diabetic population had HbA1c levels greater than 8%. Three additional studies in Malaysia reported similar results [19-21]. In contrast, an observational study in Pennsylvania reported that a majority of their study population (75%) attained HbA1c levels below 7% [22]. More than a third of the patients in this study did not achieve the target BP (<130/80 mm Hg). However, the vast majority of the hypertensive patients were also treated with anti-hypertensive drugs, which may have been a complicating factor. Uncontrolled BP may be correlated with lifestyle patterns, such as smoking or alcohol use, the patients' use of anti-hypertensive drugs, and the patients' exercise habits. The vast majority of diabetic patients in the current study had HDL cholesterol levels that were negatively associated with a risk of CHD. The average overall lipid profile in the study

population was satisfactory, as the majority of patients were receiving anti-hyperlipidaemic agents. An uncontrolled lipid profile in this study may be multi-factorial, such as diabetic co-morbidities and complications or patient non-compliance with prescribed anti-hyperlipidaemic agents, preventing the achievement of target levels.

Diabetic patients with a long history of diabetes appeared to have difficulty in controlling their glycaemic indices, and they displayed higher HbA1c levels than did patients in the other groups. Although patients with a long history of diabetes supposedly have high self-care skills, uncontrolled glycaemia may occur due to an increased resistance to medication over time. These patients may require higher doses and/or additional medications. Consistent with the current study, an investigation showed a significant difference in Hb1Ac levels between diabetic patient groups based on the duration of the disease [23]. In contrast, another group of researchers found that the HbA1c concentration was not significantly influenced by the disease duration [19]. Interestingly, we found that patient co-morbidities affect glycaemic control. Patients with no co-morbidities displayed the lowest glycaemic control. This finding is reasonable because patients with co-morbidities must manage their co-morbidities as well as the diabetes which is not easy to achieve. Other studies have reported conflicting results. For instance, Hudon and associates (2009) did not find any significant relationship between glycaemic control and the presence of co-morbidities, as measured using the cumulative illness rating scale (CIRS). In addition, El-Kebbi *et al.* (2001) demonstrated that diabetic patients with high chronic disease scores had lower HbA1c levels, suggesting that glycaemic control is not limited by co-morbidities. We also found that HbA1c levels differed between diabetic patients with no complications and those with a number of complications. Two other studies have also demonstrated an increase in the glucose level associated with an increased number of diabetic complications. Klein and Klein (1998) reported that a high plasma glucose level was associated with the increased incidence of diabetic complications. Moreover, Schellhase and colleagues (2005) found an association between glycaemic control and the progression of secondary complications in diabetic patients with an initial symptomatic diabetic complication. This result may be observed because the increase in the glucose level causes an increase in the incidence of microvascular complications [24]. The nature of type 2 diabetes requires different therapies for each stage of its progression [25]. Many severe co-morbidities and complications are related to the chronic nature of the disease [26]. These conditions affect lipid profiles as well as BP, in spite of treatment continuation and modifications. No statistically significant differences were observed in lipid profile or BP measurements between diabetic patients with various numbers of complications. Uncontrolled hypertension and dyslipidaemia co-morbidities can lead to irreversible complications associated with diabetes. Therefore, it is reasonable that the BP and lipid profiles did not differ based on the number of these complications per patient, although it may be expected to differ across different types of complications. Adler *et al.* (2000) demonstrated that macrovascular and microvascular complications are strongly associated with high BP. Similarly, Bretzel (2007) reported that hypertension in patients with diabetes mellitus increases the risk of macrovascular complications. Our study revealed differences in systolic and diastolic BP measurements between groups of diabetic patients with different co-morbidities. Patients with hypertension alone or in addition to dyslipidaemia displayed higher BP than did other patients. These findings are reasonable and are consistent with those of another study, which reported that the vast majority of diabetic patients with hypertension have uncontrolled BP [17]. Additionally, diabetic patients with dyslipidaemia alone or with hypertension presented higher levels of LDL cholesterol, TG, and total cholesterol than did other patients. However, average HDL cholesterol levels were similar in all groups of diabetic patients regardless of co-morbidity. This phenomenon may occur due to lack of patient compliance with anti-hypertensives and/or anti-hyperlipidaemic drugs, as well as the patient lifestyles and diets. The progressive nature of diabetes requires incremental changes in pharmacotherapy over the course of the disease to achieve a glucose level close to the target level. In the current study, disease duration changes oppositely with the number of patients complications and comorbidities occurrence as the disease duration increase patients with no comorbidity and complications decrease which is logical; as the disease duration increases, the proportion of patients with no complication decreases as they become patients with complications. Previous studies have found that the incidence of co-morbidity increased significantly with disease duration [27]. Furthermore, the incidence of microvascular-related diseases significantly increased with the duration of disease [27]. A second study, by Arslantas and colleagues (2008), reported a significant positive correlation between the duration of diabetes and the incidence of complications.

CONCLUSION

There were significant difference in glycaemic control in relation to the diabetic complications in addition to the obvious differences in the number of complications and comorbidities occurrence as the disease progressed. These findings have important implications to practice specially related to counseling and education of patients with type 2 diabetes mellitus on compliance to drug therapy. These differences may not necessarily reflect the failure of the other treatment regimens recommended by the Malaysian Clinical Practice Guidelines. Rather, these findings could be due to the progression of the disease and possibly inadequate patient compliance.

The major limitation of this study is its observational nature; investigators were unable to determine patient compliance to drug therapy and diet. The study was carried out in a single centre and may not represent the other centres in Malaysia. Since the practice and adherence to clinical practice guidelines may vary from one institution to another.

ETHICS COMMITTEE APPROVAL

This study was reviewed and approved by the Clinical Research Centre (CRC) at the Penang General Hospital (registration number: 2007/70). For this type of study formal consent is not required.

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