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ORIGINAL ARTICLE

Association between polypharmacy and glycemic control among Type II diabetic patients in Phatthalung province

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ABSTRACT

Taking polypharmacy for glycemic control is continuously increasing among diabetic patients during treatment. The purpose of this study was to investigate the association between polypharmacy and glycemic control among diabetic patients. This was hospital-based prospective study. In total, 20,809 diabetic patients were diagnosed by physicians. Of these, 8,322 diabetic patients were enrolled in this study from January to December 2015. Multiple logistic regression analysis was performed to investigate the association between polypharmacy and glycemic control. Subjects who took 5 or more medicines were less likely to control their HbA1C level (Odds ratio [OR] = 0.78; 95% confidence interval [CI], 0.71 - 0.87), and subjects who took 2 or more diabetic medicines were 2 times more likely to control their HbA1C level (OR = 2.19; 95% CI, 1.99 - 2.41). In conclusion, total polypharmacy was associated with a reduction of HbA1C level. Furthermore, diabetic polypharmacy was also associated with controlling of HbA1C level. The study findings suggest that patients on polypharmacy should be intensively monitored for uncontrollable HbA1C level. In addition, comprehensive holistic care and rationale drug use should be concerned.

Key words: polypharmacy, glycemic control, diabetic patients, HbA1C

INTRODUCTION

At present, chronic diseases are a major health problem globally, particularly diabetes mellitus, commonly referred to as diabetes, a group of metabolic disorders that result in high blood sugar.
Physiologically, it is due to the pancreas either not producing enough insulin or not responding properly to the insulin. Diabetes is a top-ranked morbidity that is caused by

changing lifestyle conditions[1] such as high-carbohydrate and sweet food consumption, lack of exercise, and presence of high stress.[2]

The prevalence of diabetes is predicted to increase among world population aged 20–79 years from 8.3% in 2013 to 10% in 2035.[1] The highest proportion of diabetes is in the Asia-Pacific region.[1] In Thailand, the prevalence of diabetes was 6.9% in males and 7.7% in females.[3] The morbidity rate increased from 968.22 to 1,050.05 and 1,081.25 per 100,000 population in 2011 to 2013, respectively.[4] Additionally, it was a major cause of hospital admission (12.60%)[5] and increased the expenditure of treatment and care (0.03% of the national growth development product).[6-7]

Glycemic haemoglobin A1C (HbA1C), referred to as glycated HbA1C, is a protein within the red blood cells containing plasma glucose. Clinically, measuring HbA1C level is an overall indicator of the average blood sugar levels in the body over a period of time.[8] Uncontrollable HbA1C levels associated with physiological degeneration[9], particularly in the elderly diabetic patients[10-12], causes physiological dysfunction and results in the following complications (UKPDS, 1998): retinopathy, neuropathy, nephropathy, peripheral vascular disease, and cerebrovascular disease.[8] The higher the blood sugar level or HbA1C, the more diabetic medicines are needed to reduce the abovementioned problems and complications.

Patients may have received many medicines to control blood sugar levels or prevent comorbidity during diabetic illness. Taking polypharmacy seems to be continuously increasing among diabetic patients during treatment.[13-14] However, prior to prescribing diabetic medicines[15], patients need to modify their lifestyle conditions.[8] The adverse effects of polypharmacy may cause drug-related problems (DRPs), adverse drug reactions, and drug interactions.[13] Furthermore, using polypharmacy is associated with unreasonable prescriptions.[16-17] Its problems are relevant to physiologically degenerate and reduced metabolic functions[18] that lead to DRPs.[13]

Little is known about the association between polypharmacy on glycemic control. Epidemiological studies have revealed that polypharmacy is associated with mortality among the elderly[19-21], bleeding in the elderly patients with venous thromboembolism[22], dementia[21,23], cardiovascular diseases[24], recurrent syncope[24], hospitalised falls in the elderly patients[26-28] and poor glycemic control.[29] However, a retrospective study[29] conducted may be prone to information bias. This is due to a small sample size that leads to the low power of the study because of a wide range of 95% confidence interval (CI)[30].

This hospital-based prospective study was conducted by using routine secondary data in hospitals and health-promoting hospitals covering the urban and rural areas in Phatthalung Province. The outcome of this study was that glycemic HbA1C data that was routinely gathered by well-trained healthcare personnel was a good indicator of glycemic control among diabetic patients. Moreover, this study involves a large database that routinely follows up diabetic patients in southern Thailand. The advantage of this study is to evaluate adverse effects of using polypharmacy among diabetic patients. This study aimed to investigate the association between polypharmacy and glycemic control among diabetic patients in the Phatthalung Province, southern Thailand.

METHODS

This hospital-based prospective study was conducted in diabetic patients registered in the Phatthalung Chronic Link Database and 43 folders of Structural Standardised Database performed by hospitals and health-promoting hospitals monitored by Phatthalung Provincial Health Office, Phatthalung Province, Thailand. These two databases were merged in this study.

The study subjects were enrolled who attended at first visits during January and December 2015. The subjects were routinely observed at 4 months for their following up treatment. In total, 20,809 subjects were diagnosed and confirmed by physicians as having diabetes mellitus type 2 (classified by the International Classification of Diseases, Tenth Revision, Clinical Modification, E11-E14) and were registered in the databases. However, subjects were excluded if they had no results of glycemic HbA1C level (n = 10,547) and had not received oral diabetic medicine (n = 1,940). Thus, 8,322 subjects remained and were included in this study.

The independent variable was determined as polypharmacy, which is taking a number of medicines during diabetic treatment, including diabetic and total medicines, after HbA1C was defined. Diabetic polypharmacy was defined as taking diabetic pharmacy greater than or equal to 2 medicines. Total polypharmacy was defined as taking all kinds of medicines greater than or equal to 5 medicines. The primary outcome of glycemic control was a current history of HbA1C among patients who had routine follow-ups during diabetic treatment. HbA1C levels were recorded by professional healthcare personnel, responsible for diabetic care, who were well-trained to use the database. The glycemic control was classified by HbA1C levels less than 7% as a controllable HbA1C group. Additionally, the result of HbA1C level was measured using the most recent laboratory test result during the study period.

Initially, baseline characteristics were presented as descriptive statistics. The primary outcome was glycemic control, dichotomous variable (defined as controllable HbA1C level less than 7% and uncontrollable HbA1C level greater than or equal to 7%). The variables were constructed using bivariate analysis, that is, simple logistic regression analysis, to demonstrate the factors associated with glycemic control. A three-stage modelling strategy was used. Firstly, a model was constructed for each of the baseline factors, and all important factors from the previous studies were considered. The continuous variables included both the continuous and category variables to find the best possible factors. Secondly, factors with a coefficient value for which the p-value was less than or equal to 0.25 using Wald test in the bivariate models, multiple logistic regression analysis, were considered and entered into the initial model. Using a backward elimination method, the factors with p-value greater than 0.05 using the Wald test were eliminated. However, these factors were not excluded from the initial model because they were considered as the confounding factors.

The results of this study were presented as odds ratio (OR) with 95% CI. The result was interpreted as having no association if the OR was 1, as having a risk association if the OR was greater than 1, and as having a protective effect if the OR was less than 1.

Ethical approval to use the data was obtained from and the study approved by the Ethics Committee on Human Rights Related to Human Experimentation, Phatthalung Provincial Health Office, Phatthalung Province, Thailand (Ref. No: PT 0032/59; 4 May 2016).

RESULTS

The demographic factors among diabetic patients in Phatthalung Province revealed that two-thirds of them were female (65.73%), and their average age was 62.86 (standard deviation [SD] = 17.97) years. More than half of them were agriculturists (53.97%) and one-third of them were employees (26.79%), respectively. The proportion of glycemic control among diabetic patients revealed that one-third of them had controllable HbA1C levels (35.37%). Furthermore, the polypharmacy among subjects showed that half of them received two or more diabetic medicines. The average of receiving diabetic medicine was 1.60 (SD = 0.58) medicines. Moreover, more than half of them received five or more total medicine (56.91%), and the average total number of medicines received was 5.35 (SD = 2.64) medicines. The demographic factors and the proportional of glycemic control have been published elsewhere (Rakkleng *et al*., 2017).

The bivariate analysis of factors associated with glycemic control among subjects was found as shown in Table 1. Results showed that sex, body mass index (BMI), duration of diabetic illness, and use of diabetic medicines were statistically significant with respect to glycemic control. Female subjects were 1.22 times more likely to be able to control HbA1C level compared to males (OR = 1.22; 95% CI, 1.12 - 1.33). Subjects whose BMI ranged from 18.50 to 22.99 kg/m^2 were 1.26 times more likely to be able to control their HbA1C level (OR = 1.26; 95% CI, 0.96 – 1.66), and subjects whose BMI was more than or equal to 23 kg/m^2 were 1.50 times more likely to be able to control their HbA1C level (OR = 1.50; 95% CI, 1.29 – 1.74) compared to those who had BMI less than 18.50 kg/m^2. Furthermore, subjects who had a diabetic illness for more than or equal to 7 years were 1.29 times more likely to be able to control their HbA1C level compared to those who had a diabetic illness for less than 7 years (OR = 1.29; 95% CI, 1.15 - 1.44). Furthermore, subjects who received 2 or more diabetic medicines were 2 times more likely to be able to control their HbA1C level compared to those who received 1 diabetic medicine (OR = 2.07; 95% CI, 1.88 - 2.27).

Table 1 Crude analysis of factors associated with glycemic control among diabetic patients

Factors	OR	95%CI	p-value
Sex			<0.001
Male	Ref.		
Female	1.22	1.12 to 1.33	
Age (year)			<0.001
< 35	Ref.		
≥ 35	0.30	0.19 to 0.48	
Complication			0.066
No	Ref.		
Yes	1.12	0.99 to 1.26	
Comorbidity			0.024
No	Ref.		
Yes	0.74	0.58 to 0.96	

Factors	OR	95%CI	p-value
Body mass index (kg/m^2)			<0.001
< 18.50	Ref.		
18.50 - 22.99	1.26	0.96 to 1.66	
≥23	1.50	1.29 to 1.74	
Duration of diabetic illness (year)			<0.001
< 7	Ref.		
≥ 7	1.29	1.15 to 1.44	
Number of attending health care services (times)	0.94	0.93 to 0.96	<0.001
Diabetic polypharmacy			<0.001
1	Ref.		
≥2	2.07	1.88 to 2.27	
Total polypharmacy			0.019
1 – 4	Ref.		
≥5	0.90	0.82 to 0.98	

OR: Odds ratios; 95%CI: 95 Percent confidence interval

In contrary, factors that were statistically significant with the reduction of glycemic control included age, comorbidity, number of attending healthcare services, and total polypharmacy. Subjects who were 35 years or older were 70% less likely to be able to control their HbA1C level compared to those younger than 35 years (OR = 0.30; 95% CI, 0.19 - 0.48). Subjects without comorbidity were 26% less likely to be able to control their HbA1C level (OR = 0.74; 95% CI, 0.58 – 0.96) compared to those who had comorbidity. Subjects who had an increased time of attending healthcare services were 6% less likely to be able to control their HbA1C level (OR = 0.94; 95% CI, 0.93 - 0.96). Additionally, subjects who took 5 or more total medicines were 10% less likely to be able to control their HbA1C level (OR = 0.90; 95% CI, 0.82 – 0.98) compared to those who took fewer than 5 total medicines.

Multivariate analysis that was performed using multiple logistic regression analysis revealed that a total polypharmacy and diabetic polypharmacy were statistically significant with respect to glycemic control among diabetic patients. That is, subjects who took more than 5 diabetic medicines were 22% less likely to be able to control their HbA1C level (adjusted odds ratio [OR_{adj}] = 0.78; 95% CI, 0.71 – 0.87). However, subjects who took 2 or more diabetic medicines were 2.19 times more likely to be able to control their HbA1C level (OR_{adj} = 2.19; 95% CI, 1.99 – 2.41), after accounting for confounding factors such as sex, age, complication, comorbidity, duration of diabetic illness, and number of attending healthcare services as shown in Table 2.

Table 2 Multivariate analysis of the association between polypharmacy and glycemic control among diabetic patients

Factors	OR_{Crude}	OR_{Adj}	95%CI	p-value*
Total polypharmacy				< 0.001
1–4	Ref.	Ref.		
≥ 5	0.90	0.78	0.71 - 0.87	

Factors	OR_{Crude}	OR_{Adj}	95%CI	p-value*
Diabetic polypharmacy				< 0.001
1	Ref.	Ref.		
≥ 2	2.07	2.19	1.99 - 2.41	
Sex				< 0.001
Male	Ref.	Ref.		
Female	1.22	1.26	1.14 - 1.40	
Age (year)				0.003
< 35	Ref.	Ref.		
≥ 35	0.30	0.43	0.24 - 0.75	
Complication				0.196
No	Ref.	Ref.		
Yes	1.12	1.10	0.95 - 1.27	
Comorbidity				0.411
No	Ref.	Ref.		
Yes	0.74	0.87	0.63 - 1.21	
Duration of diabetic illness (year)				0.013
< 7	Ref.	Ref.		
≥ 7	1.29	1.18	1.04 - 1.35	
Number of attending healthcare services (times)	0.94	0.95	0.94 - 0.97	<0.001

*OR: Odds ratios; OR_{crude}: Crude odds ratios; OR_{adj}: Adjusted odds ratios; 95%CI: 95 percent confident interval; * Partial likelihood ratio test*

DISCUSSION

In this study, one-third of the subjects were classified as having glycemic control (35.37%). It is possible that most of the subjects were the elderly (mean ± SD, 62.86 ± 12.17), who are a group of people having physiological degeneration that likely leads to dysfunction of the metabolism of the pancreas and liver.[32] It indicated that it is difficulty in controlling HbA1C level among aging people who had diabetes. This study was relevant to the reports of Thai glycemic control that only one-third of type II diabetic patients with hypertension were able to control their HbA1C level (36.30%) and about one-fourth among diabetic patients in Bangkok, Thailand (23.91%).[33] Furthermore, the American retrospective study conducted by Willey *et al.*[29] revealed that only one-fourth of diabetic patients were able to control their HbA1C level (25.00%).

Half of the subjects took 2 or more diabetic medicines (55.08%). Usually, the second medicine will be prescribed due to unable to control HbA1C level (>9%) or have fasting blood sugar (FBS) greater than 220 mg/dl.[8] Our study showed that two-thirds of subjects were uncontrolled their HbA1C level (64.63%). Therefore, those subjects were treated and prescribed more than one diabetic medicine. This is similar to the results of Thai Medical Research Networks, which reported that half of the diabetic patients with hypertension took 2 or more diabetic medicines (45.87%).[34] Additionally, the study by Noale *et al.*[35] in Italy revealed that half of type II diabetic patients took 2 or more diabetic medicines during treatment (50.50%). However, the study by Manakitjongkol[36] revealed that three-fourths of diabetic patients took 2 or more diabetic medicines.

Referring to total polypharmacy, half of the subjects took 5 or more medicines during treatment. Most of them were the elderly (62.86 ± 12.17) and had comorbidity (87.91%), so it is possible that they were prone to receive many medicines during treatment. Those were ageing people and had comorbidity which was chronic diseases. Consequently, it results in receiving multiple medicines during their diabetic treatment. This study is relevant to the study by Manakitjongkol[36] that presented that an average number of total medicines taken was 5.05 (SD = 2.10). Additionally, the study by Huri and Wee[37] in the University of Malaya Medical Center showed the total average number of diabetic medicines taken was 6.90 (SD = 2.80) among diabetic patients with hypertension. Furthermore, the study by Huang *et al*.[26] showed that one-third of diabetic patients took 5 or more medicines (37.67%) with an overall average number of diabetic medicines taken as 4.16 (SD = 3.27).

The multivariate analysis revealed that total polypharmacy was statistically significant with respect to glycemic control among diabetic patients, that is, subjects with total polypharmacy associated with a reduction to control their HbA1C level (OR = 0.78; 95% CI, 0.71 – 0.87). It is possible that most subjects had comorbidity (87.91%), which increased the use of polypharmacy during their treatment. Additionally, an adverse effect of pharmacokinetics using polypharmacy during treatment may have occurred. The metabolism, absorption, distribution, and excretion were pharmacologically decreased among the elderly.[32]

In contrary, subjects with diabetic polypharmacy were 2 times more likely to be able to control their HbA1C level (OR = 2.19; 95% CI, 1.99 – 2.41) after accounting for confounding factors. It is possible that diabetic patients who are unable to control their HbA1C level will continuously be treated by additionally taking diabetic medicines as a clinical practice guideline of diabetes mellitus in order to decrease HbA1C level.[8] Consequently, it reported that those were able to control their HbA1C level.

The findings of this study are comparable to those of the retrospective cohort study conducted by Juarez, *et al.*[38] among 2,970 Hawaiian diabetic patients who showed that diabetic patients taking 15 or more medicines were 2.08 times more likely to decrease their glycemic control (HbA1C > 9%) (OR = 2.08; 95% CI, 1.23 – 3.54) compared to those taking 4 or less medicines. The study by Hartz *et al*.[39] conducted a retrospective cohort study that followed up 69 type II diabetic patients in Medical Clinic, University of Iowa, USA. It found that polypharmacy was associated with glycemic control (HbA1C ≥ 7) (p-value = 0.04).

However, this study is different from the retrospective study conducted by Willey *et al*.[29], which enrolled 4,282 American diabetic patients registered in the database, showing that subjects who took 2 oral agents were 47% less likely to be able to control their HbA1C level (OR = 0.53; 95% CI, 0.38 – 0.76) and subjects who took 3 oral agents were 80% less likely to be able to control their HbA1C level (OR = 0.20; 95% CI, 0.08 – 0.54). Moreover, the cohort study conducted by Benoit *et al*.[40], which followed up 573 diabetic patients in a medical centre in California, USA, showed that polypharmacy was associated with glycemic control (HbA1C = 12%) (estimate = 0.049, p-value < 0.001). Furthermore, the cross-sectional study conducted by Fox *et al*.[41], with 10,663 diabetic patients included in the study, revealed that diabetic patients taking 2 or more diabetic medicines were associated with glycemic control (p-value = 0.020).

This is the first study that attempted to investigate the effect of routine treatment of subjects. This study had the following strengths: this study was composed of a large sample size and had a narrow 95% CI. However, this study had several limitations. More than half of the subjects (50.68%) had no laboratory blood test results (HbA1C) during the study period. Therefore, information bias of glycemic control may have occurred and been underestimated. However, the number of subjects was large enough to quantify the results. Moreover, this study was based on the databases under the supervision of the Phatthalung Provincial Health Office, southern Thailand, so results are likely to be only generalizable to populations. Furthermore, the data used in this study were routinely gathered prior to the present analysis. The effect of possible factors on glycemic control was unaccounted for confounding factors such as food consumption and health risk behaviour.[31]

Additionally, the sensitivity analysis was performed using different HbA1C level cutoff points as glycemic control. HbA1C levels less than or equal to 6.5%, 7.5%, and 8.0% were tested. The results of the different HbA1C cutoff points are relevant.

CONCLUSIONS

In conclusion, using total polypharmacy was associated with a reduction of HbA1C level. However, using diabetic polypharmacy was also associated with controlling HbA1C level. The results suggested that subjects who took polypharmacy should be intensively monitored as they may not be able to control their HbA1C level Moreover, comprehensive holistic care and rationale drug use should be exercise.

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