

GLYCAEMIC CONTROL AND HYPOGLYCAEMIA AMONG PATIENTS WITH DIABETES IN A PHARMACIST-MANAGED INSULIN TITRATION PROGRAMME

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Published online: 23 November 2023

To cite this article: LIM, P. C., WONG, T. Y., LIM, Y. L., LIM, S. L. & LEE, C. Y. (2023) Glycaemic control and hypoglycaemia among patients with diabetes in a pharmacist-managed insulin titration programme, *Malaysian Journal of Pharmaceutical Sciences*, 21(2): 1–12, <https://doi.org/10.21315/mjps2023.21.2.1>

To link to this article: <https://doi.org/10.21315/mjps2023.21.2.1>

ABSTRACT

The impact of a pharmacist-managed insulin titration has never been systematically assessed among patients with diabetes. This study aimed to evaluate the impact of pharmacist-managed insulin titration on glycaemic control, total daily insulin dose, hypoglycaemia, hunger and body weight. Data was collected retrospectively from patients treated with insulin under the care of a pharmacist-managed insulin titration programme at the Diabetes and Endocrine Clinic, Hospital Pulau Pinang, Pulau Pinang, Malaysia. Patients who followed-up with pharmacists at one month to two months intervals and completed at least eight visits were included. Ninety-one patients (59.3% male) aged 50.82 ± 17.63 years old with 13.38 ± 8.88 years of diabetes were evaluated. Glycaemic control improved significantly from baseline to 4th month (–1.19%, $p < 0.001$) and 8th month (–1.37%, $p < 0.001$). Majority of patients were on twice daily premixed insulin (44.0%) followed by basal insulin (28.5%), basal bolus (18.7%) and thrice daily premixed insulin (8.8%). Total daily insulin dose increased significantly from baseline to 8th month among patients on basal insulin (0.24 ± 0.15 versus 0.29 ± 0.18 units/kg/day, $p = 0.008$) whereas the opposite was seen in patients treated fully on insulin (1.06 ± 0.48 units/kg/day versus 0.96 ± 0.37 units/kg/day, $p = 0.005$). Total hypoglycaemia and hunger episodes reduced significantly from 160 episodes/month to 30 episodes/month, $p = 0.001$ and 39 cases/month to 5 cases/month, $p < 0.001$, respectively, across all groups. Mean weight increased by 0.66 kg from baseline to 8th month, $p = 0.045$. Insulin dose had a positive correlation to hypoglycaemia, $r = 0.338$, $p = 0.001$. Pharmacist-managed insulin titration programme significantly improved glycaemic control and reduced hypoglycaemia occurrences.

Keywords: Pharmacist, Insulin, Titration, Glycaemic control, Hypoglycaemia

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INTRODUCTION

Diabetes is a major health concern worldwide. According to the National Health and Morbidity Survey in 2019, 18.3% of people aged 18 years old and above were living with diabetes in Malaysia. This number is expected to increase further due to obesity and the aging population (Institute of Public Health 2019). A large proportion of patients receiving treatment in Malaysian public healthcare facilities did not achieve satisfactory diabetes control. Only 12.2% and 23.8% of patients achieved target glycosylated haemoglobin (HbA1c) < 6.5% and < 7%, respectively (Mafauzy *et al.* 2013).

The management of diabetes is best achieved through a team-based approach, where physicians and other healthcare providers work together to achieve desirable treatment outcomes. Public hospitals in Malaysia manage diabetes in teams that consist of physicians, pharmacists, nurses and dieticians (Hussein *et al.* 2015). This recommended multidisciplinary approach is believed to provide cost-effective, quality, safe and patient-centred care (Ministry of Health Malaysia 2015).

Various studies in the United States and Canada demonstrated improvement in adherence and clinical outcomes in patients enrolled in pharmacist-assisted diabetes management clinics (Rochester *et al.* 2010; Pitlick and Brooks 2010; Al-Hamarneh *et al.* 2013; Al-Hamarneh *et al.* 2015). Rochester *et al.* (2010) reported that the use of a pre-planned protocol for initiation and titration of insulin by pharmacists through collaborative drug therapy management service resulted in an HbA1c reduction of 2.63% among 54 patients over a period of 6 months. Fifteen patients (28%) achieved the target HbA1c of less than 7.5% and only one patient had emergency room visit for hypoglycaemia during the study period.

Meanwhile a study conducted in Perth, Australia demonstrated that the pharmacist-led Diabetes Management Education Programme reduced hypoglycaemia episodes by half with an odds ratio of 0.54 (95% CI: 0.34, 0.86; $p < 0.01$) compared to the control group (Hendrie *et al.* 2014). In another study in the United States, HbA1c was reduced by 0.9% among patients enrolled in a pharmacist-managed insulin titration programme (Pitlick and Brooks 2010). Al-Hamarneh *et al.* (2013) showed a significant improvement in mean HbA1c from 9.1% to 7.3% among patients who were enrolled in a pharmacist-managed insulin initiation and titration service.

In Malaysia, the Diabetes Medication Therapy Adherence Clinic (DMTAC) is an outpatient service offered by pharmacists in collaboration with physicians to provide medication and disease education, monitor treatment outcome, identify and manage drug related problems in diabetes mellitus patients. DMTAC service is offered to all patients with uncontrolled diabetes with HbA1c > 8% despite optimum medications prescribed by doctors, non-adherence to medications, multiple medications, underlying co-morbidities and/or macrovascular and microvascular complications such as cardiovascular disease, cerebrovascular disease, peripheral vascular disease, nephropathy, retinopathy and neuropathy (Ministry of Health Malaysia 2014).

The ultimate aims of the service are to improve medication adherence and to achieve target glycaemic control while minimising occurrence of adverse events. To date, many studies have shown that pharmacist-led DMTAC services helped to improve glycaemic control in patients with diabetes in Malaysia. In Hospital Pulau Pinang, it was reported that mean HbA1c was reduced by 1.73% and mean fasting blood sugar (FBS) was reduced by 2.65 mmol/L in patients who completed eight visits in the DMTAC programme (Lim and Lim 2010). In a randomised controlled study in a university hospital setting, it was reported

that mean HbA1c was reduced from 9.66% to 8.47% in the pharmacist intervention group (Butt *et al.* 2016). Similarly, a randomised controlled study by Lim *et al.* (2016) in a primary healthcare setting also reported significant improvement in glycaemic control among patients treated in the pharmacist intervention group. The findings from a multicentre retrospective study in 14 government health clinics in Kuala Lumpur and Putrajaya also showed that DMTAC service improved HbA1c by 1%, besides enhancing medication understanding and adherence (Lee *et al.* 2015).

Insulin has been widely used to treat diabetes in Malaysia particularly in the government healthcare facilities and represents an integral part of diabetes care. The use of insulin among hospital-based outpatient diabetes care tripled from 23.6% in 1998 to 65% in 2013 (Mafauzy *et al.* 2013). Although there are many reports of improvement in glycaemic control with pharmacist-led DMTAC in Malaysia, the impact of pharmacist intervention particularly in monitoring and adjusting patient insulin doses towards positive clinical outcomes has yet to be explored. This study aimed to fill this gap by assessing glycaemic control, insulin dosage adjustment and adverse events related to insulin use among diabetes patients in a pharmacist-managed insulin titration programme, an integral component of the DMTAC service.

METHODS

Study Design and Setting

This was a retrospective cohort study among diabetic patients who received additional care of a pharmacist-managed insulin titration programme in addition to the usual clinic follow-up in the Diabetes and Endocrine Clinic, Hospital Pulau Pinang, Pulau Pinang, Malaysia. Patients who were not recruited in DMTAC service received treatment from the usual clinic follow-up with the physicians.

Study Population

Patients of both genders aged 18 years old and above with diabetes mellitus treated with insulin who were enrolled in the pharmacist-managed insulin titration programme and followed-up with pharmacists at 1- and 2-month intervals according to protocol by the Pharmaceutical Services Division, Ministry of Health, Malaysia (2014) were included in the study. Insulin adjustments were done every 1- or 2-month interval after patients had at least two sets of self-monitoring blood glucose (SMBG) readings. Patients who were initiated on insulin should have their dose optimised within the first few months of starting insulin. Patients who were treated solely with oral antidiabetic drugs (OAD) were excluded from the study. Diabetes control target was set for HbA1c < 7% in most patients in accordance with the Clinical Practice Guideline, Management of type 2 diabetes mellitus (T2DM) by the Ministry of Health, Malaysia (2015) and glycaemic targets by the American Diabetes Association (2018). However, in patients aged > 65 years old, individualised targets ranging from 6.5% to 8.0% were set. To ensure the impact of pharmacist's role on insulin titration and continuity of care (Ministry of Health Malaysia 2014), patients who did not complete at least eight visits with pharmacists, defaulted follow-up sessions and with incomplete data were also excluded.

Sampling Method

Sample size was calculated using one sided paired z-test using the PASS software (NCSS LLC, Utah, USA). Based on the study by Lee *et al.* (2015), with the alpha at 0.05 and the power of 0.08, there was a significant improvement in HbA1c from baseline ($p < 0.01$). Mean differences from baseline to post intervention for HbA1c and standard deviation were 1% and 1.7, respectively. Nevertheless, the sample size calculated was small. Hence, assuming a HbA1c reduction of 0.5%, a standard deviation of 1.7 and a normal distribution, a minimum sample size of 72 patients was required to reject the null hypothesis with a probability of 0.08. A total of 86 patients' records were needed considering a drop-out rate of 20%.

Records of all diabetes patients enrolled under the pharmacist care between September 2016 and September 2018 were retrieved and screened for inclusion. This group of patients had additional follow-up with the pharmacists in between the usual clinic follow-up. During the DMTAC visits, the pharmacists monitored and titrated the insulin doses based on patient's SMBG records, identified any adverse events be it self-reported or via interview during the visit, reviewed the need to refer to physician for early follow-up as well as provided education related to medication, diabetes, hypoglycaemia and hyperglycaemia signs and symptoms as well as management, diet and exercise and complications to the patients. Insulin titrations during DMTAC visits in between the usual the clinic follow-up sessions were made by the pharmacist-in-charge. On the other hand, during the usual clinic follow up with physicians, pharmacists reviewed the patients before their visit with the physicians. All interventions such as insulin dose titration and initiation, discontinuation or dosage adjustment of drugs for hypertension or hypercholesterolemia and other conditions were suggested and recorded in the patient's medical record book that served as communication to the physicians. The follow-up with physicians were usually at 4-month intervals and laboratory tests were done 1 week before the session. Insulin doses were titrated individually and targets were assessed based on the Practical Guide on Insulin Therapy, Ministry of Health Malaysia (2010).

Data of patient characteristics encompassing gender, age, ethnicity, type of diabetes, duration of diabetes, comorbidities, self-monitored blood glucose levels and insulin regime were collected. Glycosylated haemoglobin values within a month before recruitment to initiation of the insulin titration programme were collected as baseline glycaemic controls. Data of insulin doses that were adjusted and number of insulin titrations during pharmacist follow-up were also collected. Adverse effects as documented in the patients' medical record and SMBG record were collected based on the noted number of hypoglycaemia episodes (blood glucose level less than 3.9 mmol/L) (Ministry of Health Malaysia 2015; American Diabetes Association 2018) or any hospitalisation occurrences related to hypoglycaemia. The symptoms of hypoglycaemia such as shivering, cold sweat, palpitation, drowsiness and dizziness, as well as the management plan for hypoglycaemia noted on the patients' record were collected. Meanwhile, data on the presence of hunger was obtained from reports by patients during DMTAC visits noted in the patients' medical record as indicated by patients' expressing the need to eat between meals to avoid hypoglycaemia. All the data were recorded in a data collection form.

Outcome Measurements

The outcomes evaluated were differences in HbA1c and changes in total daily insulin dose at baseline, 4th month and 8th month. Parameters related to adverse events of insulin treatment, namely number of hypoglycaemic episodes and hunger pangs, and body weights were also collected at baseline and the 8th month.

Data Analysis

Data collected were analysed using SPSS version 18.0 (IBM Corporation, Armonk, New York, USA). The level of significance was set at 0.05. Descriptive statistics were used to determine the glycaemic control, insulin dose, hypoglycaemic episodes, body weight, number of drugs for diabetes treatment, number of insulin titration and total number of drugs of patients. Paired *t*-test was used to determine the differences within groups for normally distributed data while Wilcoxon signed-rank was used to analyse non-normally distributed data. The presence or absence of hunger episodes was a binary data and was analysed using Chi-square test. Correlation of insulin dose and hypoglycaemia episodes as well as weight were determined using Pearson's correlation coefficient. On the other hand, correlation of number of drugs for diabetes treatment, number of insulin titration and total number of drugs with hypoglycaemia episodes were determined using Spearman correlation.

RESULTS

Patient Characteristics

A total of 150 patient records were screened and 91 patients were included in the study. Fifty-nine patients were excluded because they did not meet the inclusion criteria (23 patients were treated solely with OAD, 20 patients did not complete 8 visits and 16 patients defaulted follow-ups). The baseline characteristics of these patients are summarised in Table 1. The patients were on a median of 2.0 (IQR = 1.0) drugs for diabetes treatment and a total of median of 6.5 (IQR = 5.0) drugs for treatment of other ailments including diabetes. There were no patients on glucagon-like peptide-1 (GLP-1) receptor agonists. Sulfonylureas prescribed to patients were either gliclazide or gliclazide modified release (MR).

Table 1: Baseline characteristics of patients.

Characteristics	Number of patients, <i>N</i> = 91
Age (years old) ^a	50.82 ± 17.63
Gender (<i>n</i> , %) ^b	
Male	54 (59.3)
Female	37 (40.7)
Race (<i>n</i> , %) ^b	
Malay	31 (31.4)
Chinese	45 (49.5)
Indian	15 (16.5)
Weight (kg) ^a	69.12 ± 14.62
BMI (kg/m ²) ^a	26.22 ± 4.79
Duration of DM (years) ^a	13.38 ± 8.88

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Table 1: (continued)

Characteristics	Number of patients, N = 91
Type of DM (n, %) ^b	
T1DM	13 (14.3)
T2DM	78 (85.7)
HbA1c (%) ^a	10.05 ± 2.31
SMBG (n, %) ^b	65 (71.4%)
Insulin regimen (n, %) ^b	
Basal + OAD	26 (28.5)
Premixed twice daily	40 (44)
Premixed thrice daily	8 (8.8)
Basal bolus	17 (18.7)
OAD (n, %) ^b	
No OAD	13 (14.3)
Metformin only	46 (50.5)
Metformin + sulfonylurea	16 (17.6)
Metformin + sulfonylurea + sitagliptin	6 (6.6)
Metformin + sitagliptin	7 (7.7)
Metformin + empagliflozin	3 (3.3)
Total daily insulin dose (IU/kg/d) ^a	
All regimens	0.82 ± 0.55
Basal + OAD	0.24 ± 0.15
Premixed twice daily	0.91 ± 0.32
Premixed thrice daily	1.22 ± 0.56
Basal bolus	1.32 ± 0.62

Notes: ^aData presented in mean ± SD; ^bData presented in frequency and percentage; BMI = body mass index; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; HbA1c = glycosylated haemoglobin; SMBG = self-monitoring blood glucose; OAD = oral anti-diabetic drugs.

Overall, glycaemic control improved significantly (Figure 1). Mean HbA1c for all patients ($n = 91$) reduced significantly from baseline to the 4th month by 1.19% (95% CI: -1.66, -0.72; $p < 0.001$) and 1.37% (95% CI: -1.87, -0.88; $p < 0.001$) to the 8th month. Slight increases in HbA1c in both the combination of basal + OAD (0.16%) and the premixed twice daily (1.00%) groups were observed within the 4th to 8th month period. However, improvements in glycaemic control in the two groups were still significant at the 8th month when compared to baseline values ($p < 0.05$). HbA1c values in the premixed thrice daily and the basal bolus groups reduced steadily from baseline to the 8th month with significant improvement in glycaemic control at the 8th month versus baseline ($p < 0.05$).

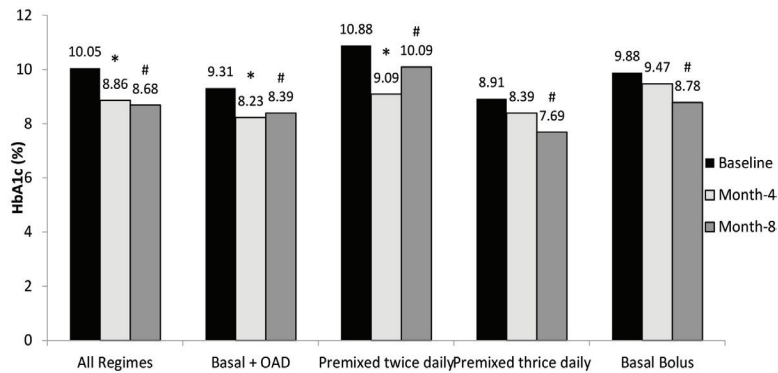


Figure 1: Mean HbA1c of treatment groups at baseline, the 4th month and the 8th month.

Notes: *significant difference between baseline versus the 4th month ($p < 0.05$); #significant difference between baseline versus the 8th month ($p < 0.05$).

Patient were categorised into basal insulin and full insulin replacement for changes in mean total daily insulin dose (IU/kg/day) based on body weight (Figure 2). Basal insulin regimen consisted of one isophane human insulin (NPH) or a long-acting insulin injection only in combination with an OAD. Full insulin replacement consisted of either premixed (30/70) twice or thrice daily or basal bolus regimens (combination of regular human insulin or rapid acting insulin and NPH insulin or a long-acting insulin). Mean total daily insulin dose increased significantly in the basal insulin group who were also treated with OAD from baseline to 8th month, indicating an increased need for insulin supplementation over time. In contrast, mean total daily insulin dose in groups given full insulin therapy decreased significantly from 1.06 ± 0.48 IU/kg/day to 0.97 ± 0.40 IU/kg/day at the 4th month and further reduced to 0.96 ± 0.37 IU/kg/day at the 8th month. The pharmacists performed a total of 553 insulin titrations (median 5.0 [IQR = 3.3]).

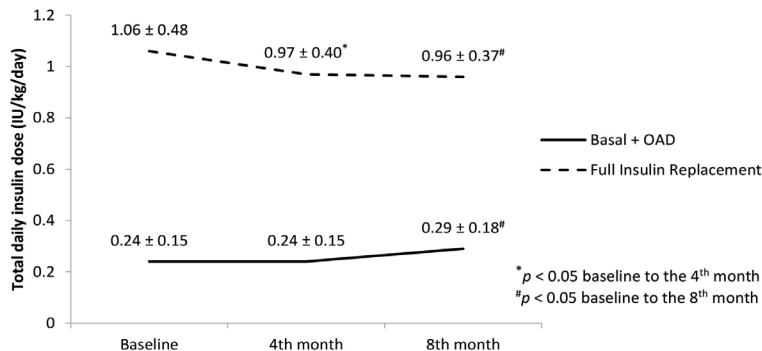


Figure 2: Changes in total daily insulin dose across 8 months of the insulin titration programme.

Adverse events related to insulin use particularly the number of hypoglycaemia episodes reduced significantly from 160 episodes (median 0 [IQR = 1]) at baseline to 30 episodes (median 0 [IQR = 0]; $p = 0.001$) at the 8th month. There were no severe hypoglycaemia episodes that required hospitalisation or emergency visit. In addition, reported incidence of hunger episodes also showed significant reduction from 30 episodes at baseline to 5 episodes at the 8th month ($p < 0.001$). However, mean body weight showed slight increase from 69.12 ± 14.62 kg at baseline to 69.78 ± 13.93 kg at the 8th month ($p = 0.045$). Insulin dose was shown to be moderately correlated to the number of hypoglycaemia episodes ($r = 0.338$, $p = 0.001$). However, there was no correlation between number of drugs for diabetes treatment ($r = 0.192$, $p = 0.070$), number of insulin titration ($r = 0.185$, $p = 0.08$) and total number of drugs ($r = 0.097$, $p = 0.363$) with the number of hypoglycaemia episodes. There was also no correlation between insulin dose and the mean weight of the patients ($r = 0.195$, $p = 0.064$).

DISCUSSION

In this study, an insulin titration programme managed by pharmacists resulted in improved glycaemic control and reduction in the occurrence of insulin-associated adverse effects namely hypoglycaemia and hunger attacks. Similarly, a study conducted among African Americans reported HbA1c reductions of 1.1% at month 6, 1.4% at month 9 and 1.3% at the 12th month follow-up when the pharmacists managed their insulin titration (Pitlick and Brooks 2010). The improvement in HbA1c could be due to more frequent insulin dose adjustments among patients enrolled in the pharmacist-managed insulin titration programme compared to routine physician's follow-up. Reduction in HbA1c was an essential target of diabetes care as it helped to achieve optimum diabetes control. This in turn would slow down the progression of the disease and reduce the risk or delay the diabetes complications.

Total daily insulin dose for patients on basal insulin with oral hypoglycaemic agents had increased at the end of the study. Pharmacists were involved in the up-titration of insulin dose especially for the patients newly initiated on basal insulin. This could be due to insulin optimisation steps taken to achieve target fasting blood glucose levels gearing towards targeted glycaemic control. According to Chan *et al.* (2017), only one-third of diabetes patients achieved HbA1c $< 7\%$ after 6 months of basal insulin therapy in Asia. Insulin optimisation was thus essential after the initiation of basal insulin to ensure satisfactory diabetes control. However, this step was often delayed due to lack of time for diabetes education and insufficient patient support system (Chan *et al.* 2017). Regular visits with the pharmacists would help to empower, motivate and ensure timely review of patients' self-monitored blood glucose so that insulin titration may be done and target fasting blood glucose could be achieved earlier in the course of the therapy.

On the other hand, total daily insulin doses were adjusted and had reduced significantly at the end of the 8-month period for patients on full insulin replacement. In the case of patients who were on full insulin replacement, pharmacist interventions included up-titration or down-titration of insulin doses to achieve the desired glycaemic target. The result demonstrated that the dose was reduced to optimal daily doses between 0.5 IU/kg/day and 1.0 IU/kg/day for most patients which generally complied with the recommended standards set by the Ministry of Health Malaysia (2010). This suggested that patients who were treated with full insulin might be over-treated with higher doses of insulin before the initiation of the insulin titration programme. In addition, the busy clinic setting with high patient load might be the factor for overlooking appropriate insulin doses during the treatment process.

Insulin overtreatment was a common problem among diabetes patients, especially in older patients. A study involving veterans in the United States suggested that half of the patients treated with insulin or sulfonylureas are potentially over-treated (Tseng *et al.* 2014). Overtreatment in diabetes is defined as tight glycaemic control and having glucose-lowering treatment including glucose-lowering agents that present high risk of hypoglycaemia such as insulin and sulfonylureas when HbA1c < 7% for patients in good health and < 8% for patients with poor health (LeRoith *et al.* 2019). For example, the use of a sulfonylurea such as gliclazide with insulin might increase the risk of hypoglycaemia. According to the Malaysian CPG T2DM 2020, gliclazide is not recommended to be used in patients with full insulin replacement. However, gliclazide is still widely used in the local public hospital setting in combination with metformin and basal insulin. This is because gliclazide is a more affordable option compared to the DPP4 inhibitors and SGLT-2 inhibitors, as well as being an effective glucose lowering agent. The risk of hypoglycaemia can be mitigated by avoiding its use in patients with history of severe hypoglycaemia, renal impairment, liver cirrhosis and elderly (Ministry of Health Malaysia 2020). Gliclazide MR with less risk of hypoglycaemia and comparable cost can also be considered a safer alternative to gliclazide (Khunti *et al.* 2020). GLP-1 receptor agonists are another alternative with lower risk of hypoglycaemia and can be considered in patients who are obese, chronic kidney disease, high risk of cardiovascular disease and heart failure (Ministry of Health Malaysia 2020). However, GLP-1 receptor agonists are not listed in the Malaysian Drug Formulary in Ministry of Health facilities currently. Hence, this drug is less accessible to the patients unless special approval is obtained. With more frequent appointments with patients, pharmacists would serve as a regular contact point between patients and other healthcare professionals. This would enable pharmacists to identify symptoms of overtreatment, which would then prompt treatment de-intensification (Patel, Triplitt and Trujillo 2019).

Unlike normal practice whereby insulin doses were only adjusted during outpatient clinic follow-up at every 3- to 6-month interval, the pharmacist-managed insulin titration programme adjusted insulin doses in between the follow-up sessions. This resulted in improvement in glycaemic control while reducing hypoglycaemic episodes as well as the incidence of hunger episodes (Harper *et al.* 2016). The patients enrolled in the programme demonstrated significant reduction of these two common adverse effects among insulin users. These results were consistent with the findings of Pitlick and Brooks (2010), where frequent pharmacist follow-ups helped to address specific patient issues such as inadequate and/or non-adherence to medications, besides minimising adverse effects such as hypoglycaemia and hunger episodes.

The results of the study indicated that the rate of hypoglycaemia was higher in patients with higher insulin dose. This was further supported by a study conducted by Rubin *et al.* (2011) which reported higher odds of hypoglycaemia regardless of the type of insulin in patients on higher, weight-based insulin doses.

Several limitations are to be noted in this study. Firstly, it involved a limited number of patients in the specialist endocrine clinic of Hospital Pulau Pinang. Therefore, the results were not generalisable to the general population as majority of the patients received diabetes treatment from primary healthcare providers (Institute of Public Health 2019). Besides, this was a retrospective study by which the data collection was solely on one cohort, based on medical records and there was no control arm as data of patients not recruited into the DMTAC service was not included. Hence, the causation could not be conclusively drawn from the data and other confounding factors contributed by other healthcare providers were unknown. However, the results of this study provided important insights into the role of pharmacists in diabetes management, particularly in insulin dose titration and minimisation

of adverse effects related to insulin use. Future randomised controlled studies that involved large numbers of patients from multiple healthcare facilities are warranted to provide more concrete evidence.

CONCLUSION

The present findings have emphasised a vital role of pharmacists in insulin titration programmes to significantly improve glycaemic control and reduce adverse events of hypoglycaemia and hunger episodes, thereby improving insulin therapy outcome. Pharmacist-led programme is available nationwide in public healthcare facilities. Therefore, pharmacists need to be actively engaged in patient care especially in newly initiated insulin cases to optimise the insulin doses as well as assist in down-titration of insulin dose in potential cases of over-treatment. Besides, the role of telemedicine and mobile apps may increase the accessibility of patients to education related to diabetes and to titrate insulin for patients remotely.

ACKNOWLEDGEMENTS

The authors thank the Director General of Health, Ministry of Health Malaysia for the permission to publish.

ETHICS APPROVAL

This research is registered with the National Medical Research Register, Malaysia (No. NMRR-18-1393-42263) and approved by the Medical Research Ethics Committee, Malaysia.

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