Diabetes, Metabolic Syndrome and Obesity

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CLINICAL TRIAL REPORT

# The Impact of Insulin Staging in the Context of Pharmaceutical Care on Patients with Type 2 Diabetes Mellitus

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**Purpose:** The problem of polypharmacy and the nature of the disease make patients with type 2 diabetes mellitus highly vulnerable to drug therapy problems, especially those who are on insulin therapy. Despite this challenge, reaching the desired clinical outcome and using an appropriate insulin regimen are also considered a controversial issue among clinicians. The current study is designed to explore the impact of insulin staging regimens in the context of pharmaceutical care on patients with type 2 diabetes mellitus.

**Patients and Methods:** This study is a randomized interventional comparative study of a few groups. It was conducted at the Diabetes and Endocrine Centre in Sulaymaniyah City in Iraq from January to August 2022. Patients with T2DM who were on insulin therapy were enrolled in this trial. The participants were divided into two groups, the interventional and non-interventional groups. The insulin regimen was modified, and pharmaceutical care process was performed for the intervention group. Drug therapy problems (DTPs) and clinical parameters were monitored both groups over the course of six months.

**Results:** A total of 67 patients with T2DM on insulin were included in this study, and of them, 73% were females, with a mean age of 57.34 ± 7.825 years. The groups were randomly divided into intervention and non-intervention groups. After six months of applying insulin staging in the context of pharmaceutical care, FPG (Mean Diff.= 72.25, 95% CI of diff.= 20.44 to 124.1), HbA1c (Mean Diff.= 2.087, 95% CI of diff.= 1.151 to 3.023) and DTP were significantly improved in the intervention group.

**Conclusion:** Implementing the insulin staging approach within the context of the pharmaceutical care process showed a significant impact on controlling plasma glucose levels.

**Keywords:** drug therapy problem, clinical pharmacy, insulin staging, adherence, insulin regimen

## Introduction

Currently, diabetes mellitus (DM) poses a challenge to world health. Due to diabetes, one person dies every five seconds. Nearly half a billion (537 million) individuals (20–79 years) have diabetes mellitus. This number is expected to reach 783 million by 2050.[1] In 2021, only in Iraq, more than 10.7% of adults are living with diabetes.[2] Approximately (~95%) of the diabetic case were type 2 diabetes (T2DM).[3] The problem of polypharmacy and the nature of the disease make patients with T2DM highly vulnerable to drug therapy problems (DTP), especially those who are on insulin therapy. Despite this challenge, achieving the desired clinical outcome and using an appropriate insulin regimen are also considered controversial issue among clinicians.

At some points of their life, a significant number of patients with type 2 diabetes will require to take insulin therapy as their beta-cell activity falls over time. Using insulin always associated with challenges, such as hypoglycemia and weight gain,[4] psychological barriers,[5] patients feeling of failure to control of their glucose level,[6] Patients' misperceptions about insulin being not effective, toxic or lead to more complications and injection pain,[7] lack of awareness,[8] dose titration and adjustment,[7] physicians lack of sufficient time for patients training and education.[9]

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Tackling all the above-mentioned problems by physicians alone is not an easy task. Many studies pointed out that clinical pharmacists can play a key role in this regard.[10–13] Adding pharmaceutical care to the health care system creates an opportunity for clinical pharmacists to manifest their roles, especially in Iraq where most of their jobs are constrained in the dispensary pharmacies.[14] Pharmaceutical care "is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life".[15] (Pharmaceutical care process steps are shown in Figure 1.)

After 100 years of insulin discovery, clinicians are still struggling to reach into an agreement on a unified insulin regimen to use for patients with T2DM.[16] A unified approach in terms of insulin regimen is a significant milestone for the management of patients with T2DM. This approach enables both clinicians and other healthcare providers to closely monitor the insulin therapy and its drug-related problems. In this study, we have tried to apply insulin staging that suggested by American Diabetic Association as a systematic and unified approach of insulin regimen.[17] Insulin staging consist of four hierarchical stages from the stage one to the stage four. Each stage has its own insulin type, frequency and ratio (as shown in Figure 2). In the current study, this systematic approach of insulin regimen was applied to the patients with T2DM in the context of pharmaceutical care process.

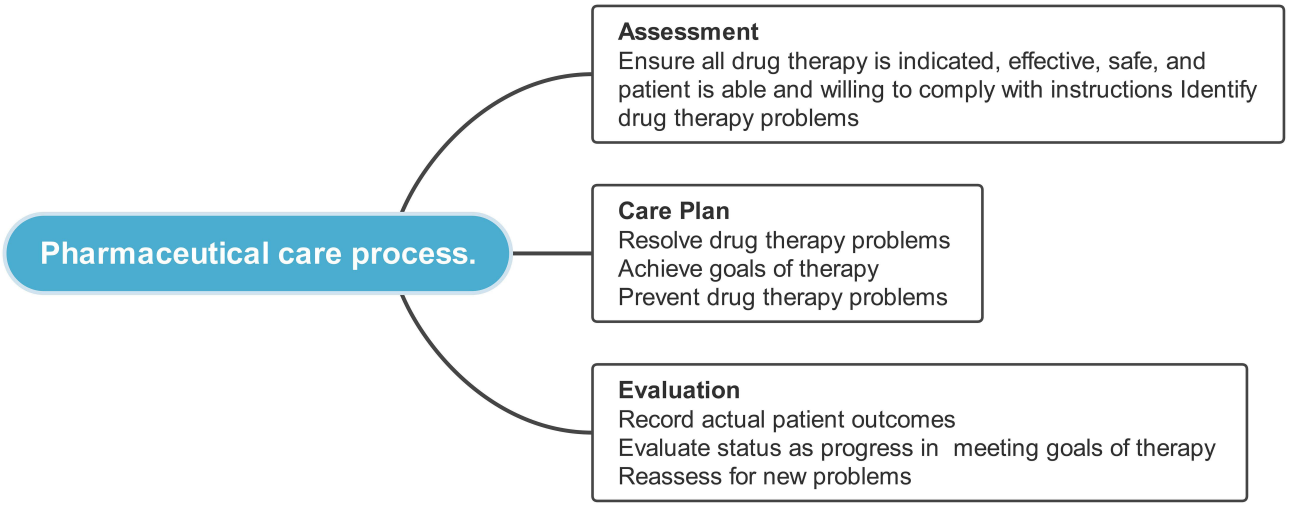


**Figure 1** Pharmaceutical care process.

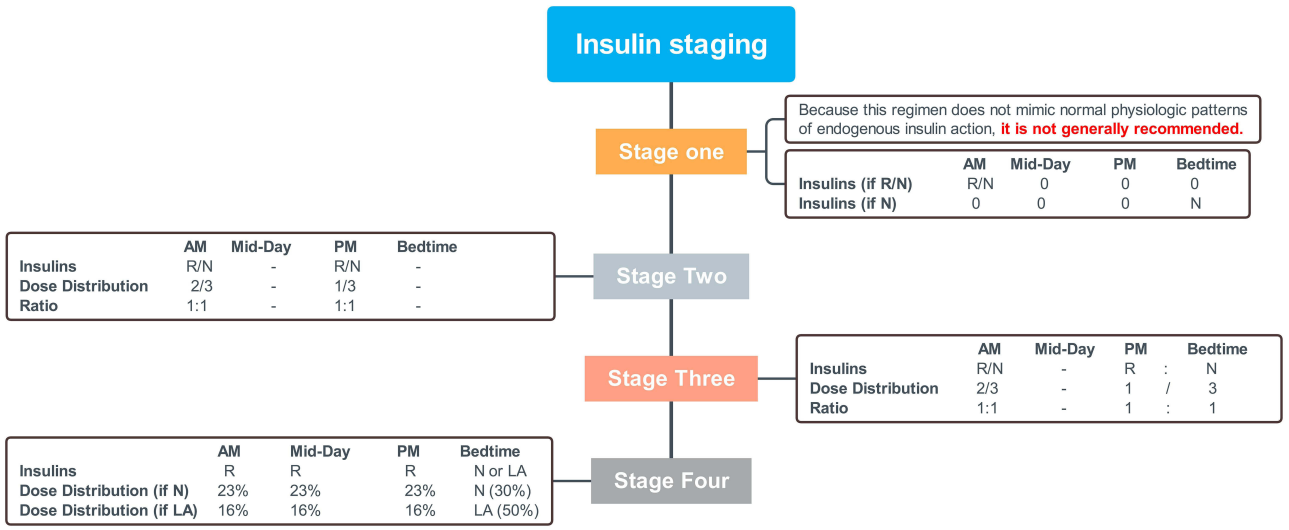


**Figure 2** Insulin staging.
**Abbreviations**: R, short acting; RA, rapid Acting; N, intermediate acting; LA, long acting.

**Table 1** Characteristics of Study Population

| Parameter | Non - Intervention Group (No. = 36) | Intervention Group (No. = 31) | *P* value |
|---|---|---|---|
| Gender (Male,%) | 9, 25% | 9, 29% | 0.7155 |
| | Mean ± SD | Mean ± SD | |
| Age | 56.61 ± 8.36 | 58.19 ± 7.19 | 0.4133 |
| Breastfeeding | 0.083 ± 0.28 | 0 | 0.1031 |
| Lean body mass[a] | 45.95 ± 8.47 | 48.09 ± 8.60 | 0.3094 |
| Height | 157.3 ± 8.943 | 160.1 ± 15.16 | 0.3552 |
| Tobacco use | 0.08333 ± 0.280 | 0.06452 ± 0.249 | 0.7742 |
| Medication allergies | 0.08 ± 0.28 | 0.16 ± 0.37 | 0.3339 |
| Adverse reaction to medication | 0.19 ± 0.4 | 0.06 ± 0.24 | 0.1236 |

**Note**: [a]Boer Formula was used to calculate lean body mass.

# Materials and Methods

## The Setting

The study design is a randomized interventional comparative study of few groups that is carried out from January 2022 to August 2022 in the Diabetes and Endocrine Centre in Sulaymaniyah City in Iraq. There is one lab, a pharmacy, and

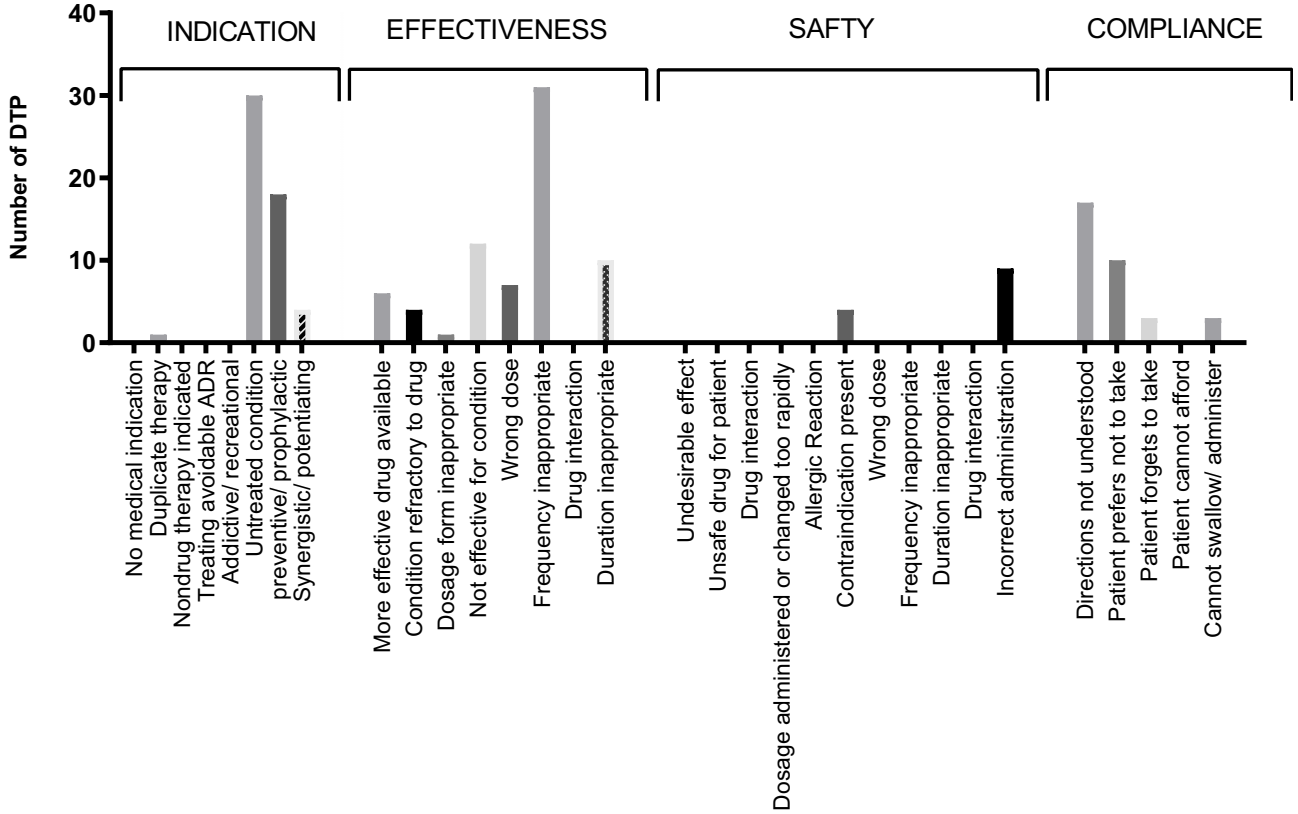


**Figure 3** DTPs among intervention group 1st visit.
**Abbreviation**: DTP, drug therapy problem.

a special section for data entry, weight, and blood pressure checking. Those patients willing to attend this study has referred by one of the physicians to the researcher.

## Ethical Considerations

- The study was approved by Ethical Committee of the College of Pharmacy – University of Sulaimani (approval number: PH 29–21).
- This study complies with the Declaration of Helsinki.
- All subjects participated voluntarily.
- All participants provided informed consent before starting the study.
- Data sharing statement: no further data will be shared because researchers had not received informed consent or ethics approval to share data (upon journal's request, we can share the data with the editor privately).

## Trial Registration

The study was registered at clinicaltrials.gov database (ClinicalTrials.gov Identifier: NCT05244200).

## Patient Selection

Seventy-three patients were enrolled to this study. All of them were previously diagnosed with T2DM and they were on insulin therapy. From the total number of patients enrolled at the beginning, only sixty-seven patients completed the study, while six patients lost in the follow-up period.

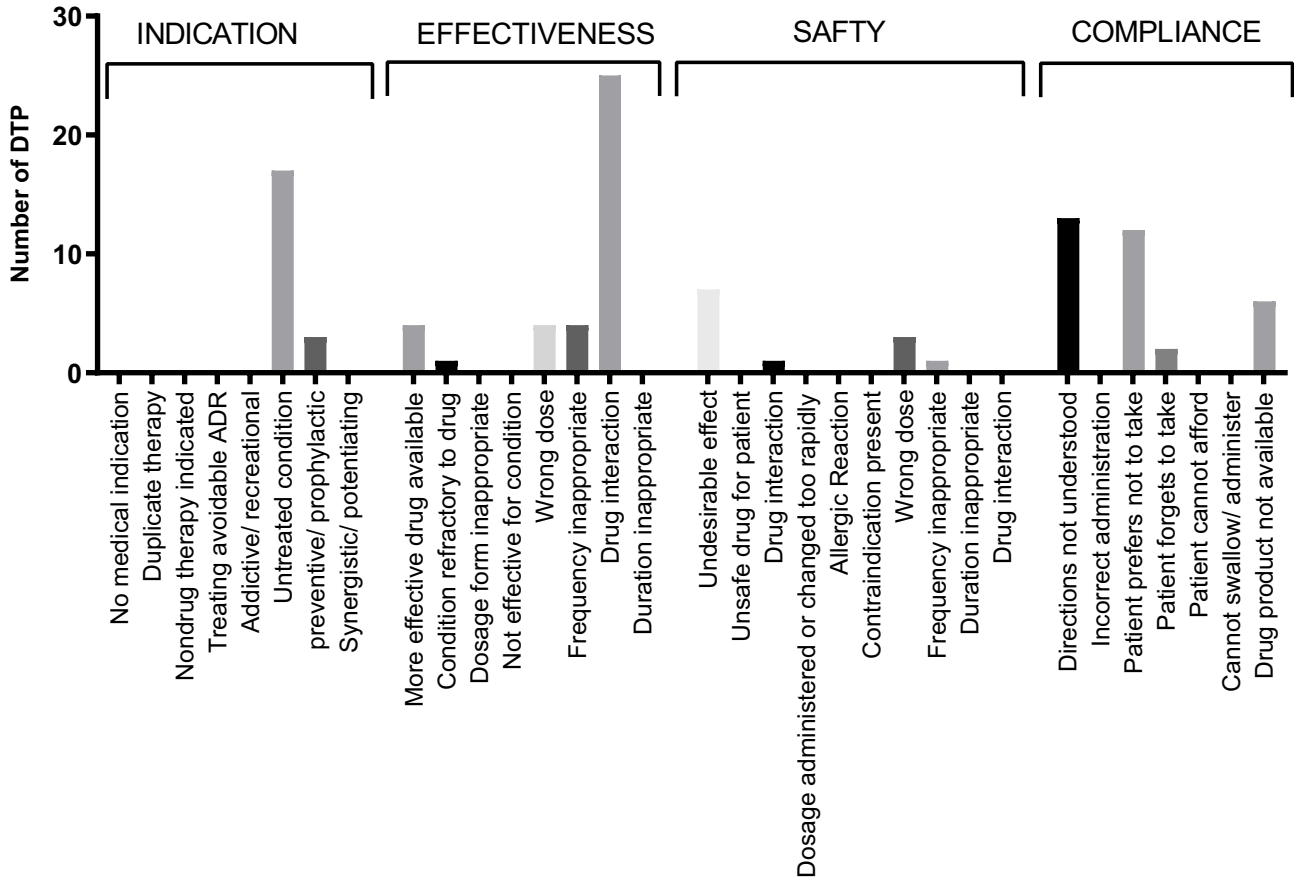


**Figure 4** DTPs among intervention group 2nd visit.
**Abbreviation**: DTP, drug therapy problem.

Patients were assigned into two groups, intervention group and non-intervention group. Thirty-three patients were enrolled in the intervention group. These patients were receiving insulin staging and pharmaceutical care process. Evaluation and follow-up were performed at baseline for fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum level of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG). Later on, these parameters were measured every three months. In terms of pharmaceutical care, intervention was performed in four main categories of DTPs, i.e. indication, effectiveness, safety and compliance. These four main categories were further divided into thirty-four subcategories as indicated in Appendix 1. These problems were monitored on monthly basis. Researchers had a cumbersome work around to detect, prevent and resolve DTPs.

While, in the non-intervention group, thirty-six patients were enrolled. Patients in this group were receiving a non-unified approach of insulin regimen. They were receiving conventional medical care. DTPs were followed up without intervention. The following parameters were also monitored at the beginning and every three months intervals: FPG, HbA1c, serum level of TC, LDL, HDL, TG.

## Data Collection

Information regarding the demographic characteristics, disease record, and past medication history were gathered from patients. Laboratory data (FPG, HbA1c, cholesterol, TG, LDL and HDL) were gathered from Diabetes and Endocrine Centre database program and then, six months pharmacist intervention were performed and DTPs were identified in both groups using UpToDate system (The UpToDate system is an evidence-based clinical resource), ADA (American Diabetes clinical guideline for the treatment of DM. Robust DTPs performed for the intervention group via implementing

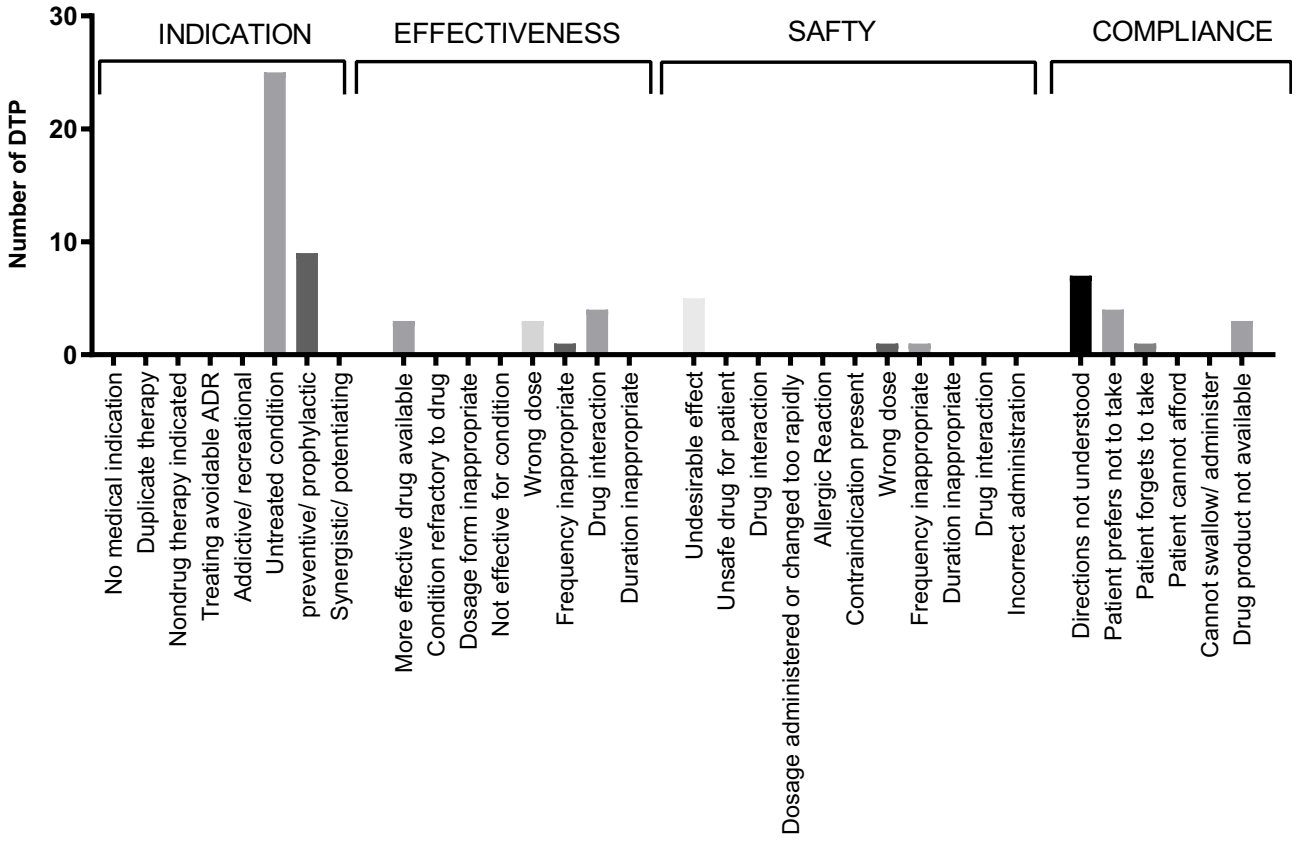


**Figure 5** DTPs among intervention group 3rd visit.
**Abbreviation**: DTP, drug therapy problem.

pharmaceutical care described by Cipolle et al to show the impact of DTP resolution on the above-mentioned parameters. The patient information sheet includes all the details recorded for those who were clinically diagnosed to have type 2 diabetes.

## Inclusion and Exclusion Criteria

### Inclusion Criteria

(a) Patients with T2DM.
(b) Patients must be on insulin therapy.
(c) Willing to participate in the study.

### Exclusion Criteria

(a) Patients with type 1 diabetes.
(b) Type 2 diabetes patients who are not on insulin therapy.
(c) Patients that have disabilities that interfere with compliances towards medications.

## Sample Collection

Venous blood about (5–8 mL) was obtained by vein puncture of each individual (intervention and non-intervention) in the same daily hours (between 8:00 and 10:30. a.m.) after overnight fasting (8–12 hours). Blood samples were transferred into gel and clot activator tube and after coagulation, they were centrifuged at 4000 rpm and the separated serum samples was then inserted into plain tubes and stored at −35°C until time for laboratory analysis.

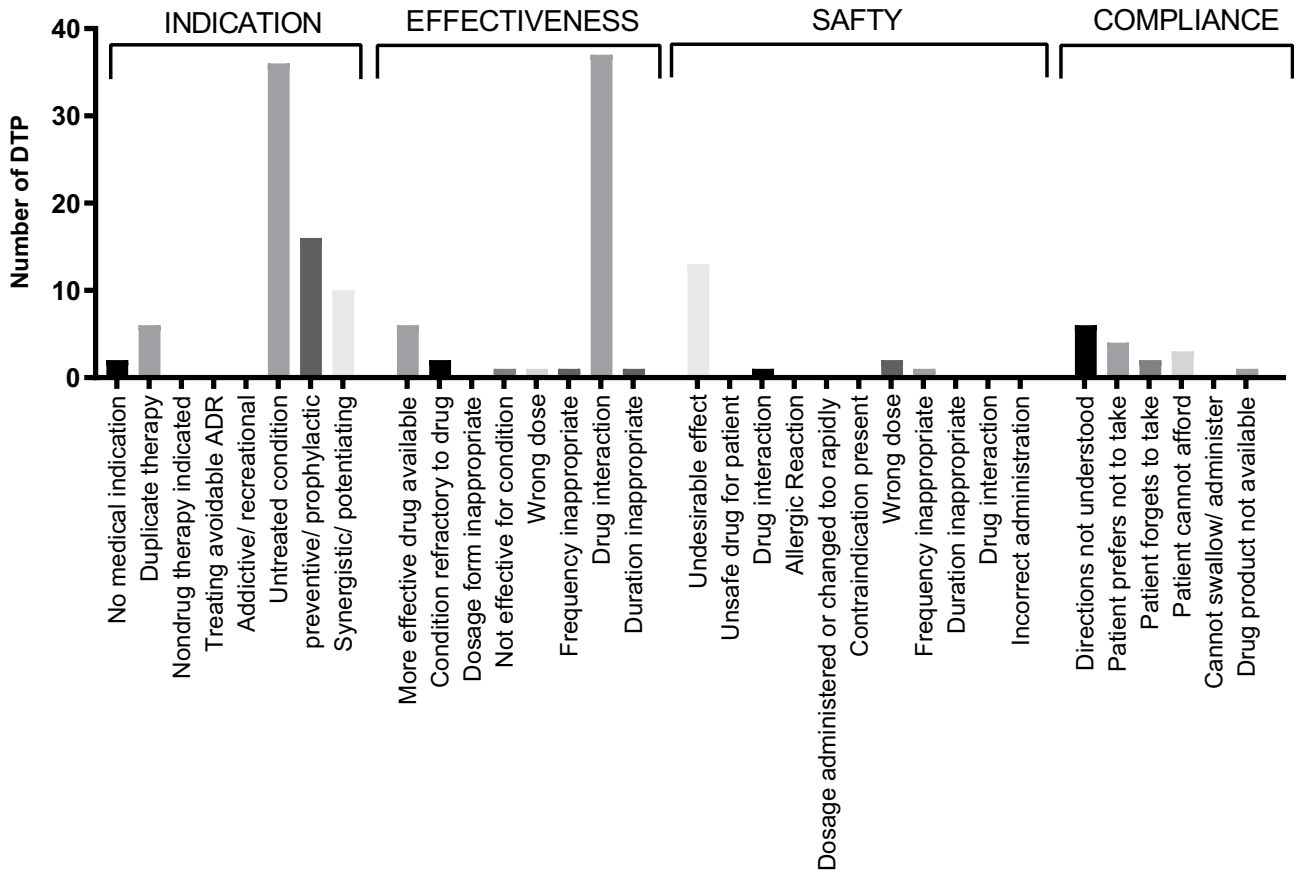


**Figure 6** DTPs among non-intervention group 1st visit.
**Abbreviation**: DTP, drug therapy problem.

## Measurement of Body Mass Index (BMI) and Waist Circumference

The international categorization of weight depending on BMI was used to evaluate the degree of obesity. By dividing weight of each patient by patient's squared height in meters, BMI was calculated:

- Underweight (BMI < 18.5 kg/m$^2$).
- Normal weight (BMI 18.5–24.9 kg/m$^2$).
- Overweight (BMI 25–29.9 kg/m$^2$).
- Obese (BMI 30 kg/m$^2$).

## Statistical Analysis

The data collection was completed, and the questions of the study were coded. Then data entry and analysis were performed. Data entry was carried out by using an Excel spreadsheet and then the statistical analysis was performed by GraphPad Prism, version 8.

Different types of bar charts (component bar charts) and line graphs were used to describe the variables of the study diagrammatically. Any $p$-value < 0.05 considered to be significant statistically.

# Results

## Patient Characteristics

Seventy-three patients were enrolled in the study at the Diabetes and Endocrine Centre in Sulaymaniyah City in Iraq. Out of this number, only 67 patients were remained until the end of the study. Characteristics of the patients, including medication allergies and adverse reactions to medications, are presented in Table 1.

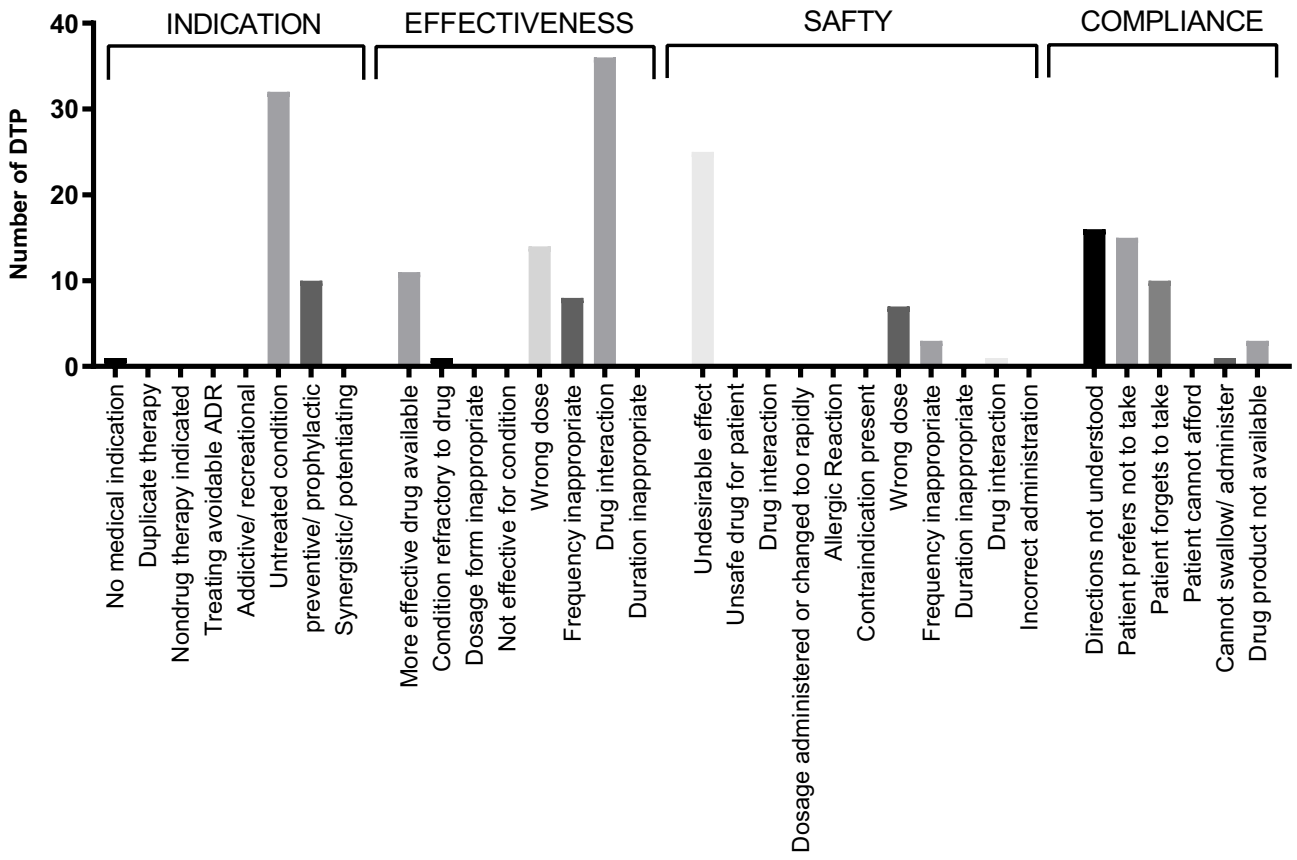


**Figure 7** DTPs among non-intervention group 2nd visit.

## Drug Therapy Problems Among Both Groups at Different Intervals

The total drug therapy problems for the intervention group per three consequent visit, i.e. 1st, 2nd and 3rd visits are showed in Figures 3–5, respectively. Upon comparison of these results with their pair ones in the non-intervention group, as showed in Figures 6–8, it is evident that most of the DTPs were located in the effectiveness and indication categories followed by compliance and safety one. At the same time, the problems related to the category of effectiveness showed to be tackled significantly in the intervention group (decreased from 61 DTPs in the 1st visit to 11 DTPs in the 3rd visit).

As presented in Figure 9, after 6 months of intervention, there was a significant reduction in the DTPs of the intervention group (P-value < 0.0001****).

## The Impact of Insulin Staging and Pharmaceutical Care on Plasma Glucose Level, Body Weight, and Lipid Profile

After the implementation of our unified insulin approach plus the pharmaceutical care process, HbA1c (Figure 10) and FPG (Figure 11) were significantly improved in the intervention group (P-value < 0.05). While the same parameters in the non-intervention group showed no significant changes as shown in Figures 12 and 13 respectively. Changes in BMI (Table 2) were insignificant in both groups. Throughout our study, the lipid parameters in both groups showed non-significant changes as well (as shown in Figure 14).

# Discussion

In this study, we report the experience of applying insulin staging on patients with T2DM in the context of pharmaceutical care in Iraq. To the best of our knowledge, this is the first research of its type to be applied in

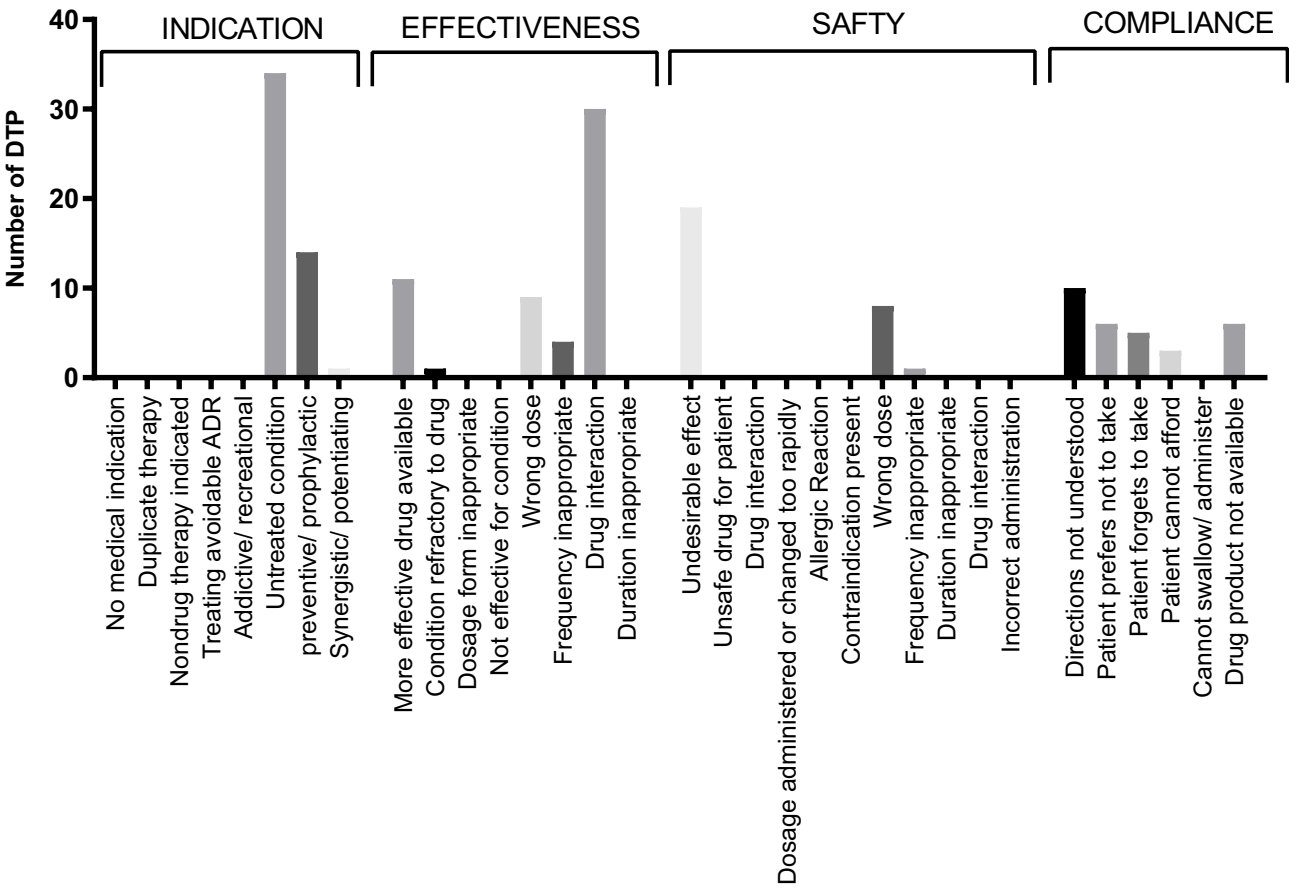


**Figure 8** DTPs among non-intervention group 3rd visit.
**Abbreviation**: DTP, drug therapy problem.

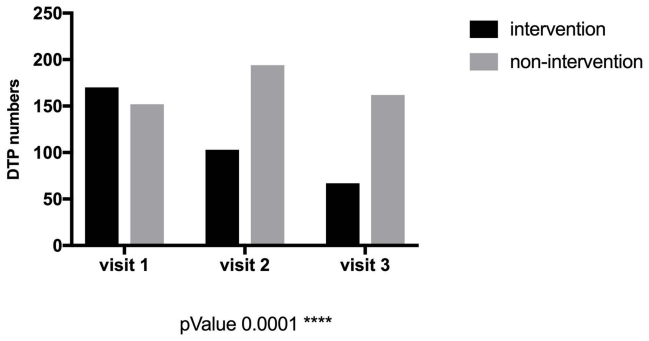


**Figure 9** DTP change in intervention and non-intervention group.
**Abbreviation**: DTP, drug therapy problem.

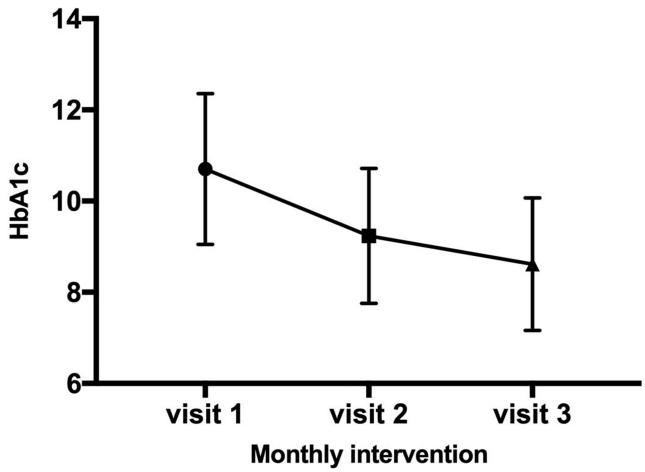


**Figure 10** Changes in HbA1c among the intervention group.
**Abbreviation**: $HbA_1c$, glycated hemoglobin.

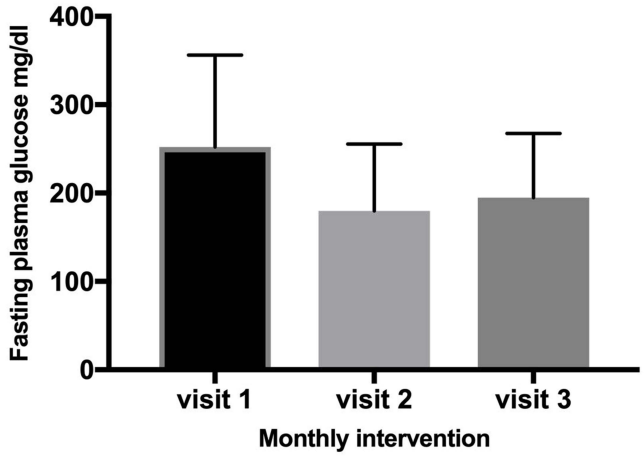


**Figure 11** FPG changes among the intervention group.
**Abbreviation**: FPG, fasting plasma glucose.

the Middle East. The participants, who were insulin-treated patients with T2DM, were divided into non-intervention (36 patients) and intervention (31 patients) groups. We ought to explore the impact of insulin staging in the contest of pharmaceutical care on clinical outcomes. The division process was random and there was no significant

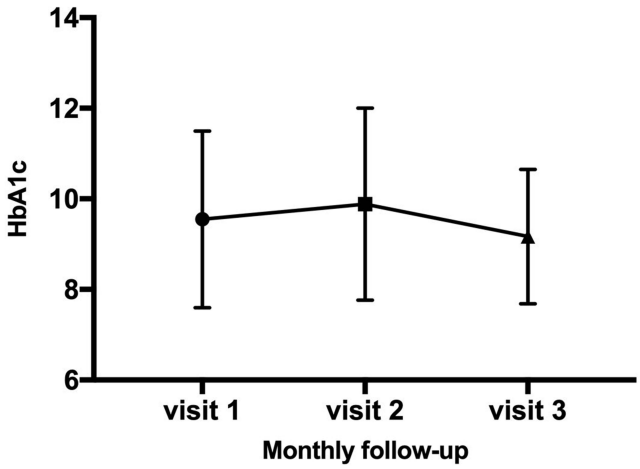


**Figure 12** Changes in HbA1c among the non-intervention group.
**Abbreviation**: $HbA_1c$, glycated hemoglobin.

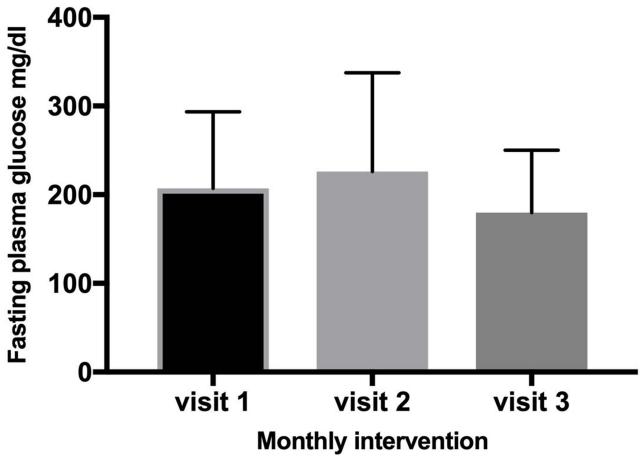


**Figure 13** FPG changes among the non-intervention group.
**Abbreviation**: FPG, fasting plasma glucose.

difference between groups in terms of demographic characteristics as demonstrated in Table 1. Our study revealed that applying pharmaceutical care and insulin staging approach by clinical pharmacists in collaboration with physicians have a significant positive impact on reducing drug therapy problems and improving therapeutic outcomes. These results suggested that clinical pharmacists can play a key role in solving DTPs. Similar findings have been reported in other studies.[18–20] Pharmaceutical care work has three main steps (as shown in Figure 1) including assessment, care plan and evaluation. To apply these steps in our study, first the assessment form, called pharmacotherapy workup table (Appendix 2), which is described by Cipolle et al,[21] was filled out by the pharmacist for every patient in both groups. In line with other studies, our assessments showed that patients with T2DM are at high

**Table 2** Change in Body Mass Index (BMI) Over 6 Months

| Groups | Visit 1 (Mean ± SD[a]) | Visit 2 (Mean ± SD) | Visit 3 (Mean ± SD) | *P* value |
|---|---|---|---|---|
| Non-intervention | 29.97 ± 5.111 | 29.71 ± 4.752 | 29.53 ± 4.733 | 0.1613 |
| Intervention | 31.17 ± 15.75 | 31.00 ± 15.57 | 31.07 ± 15.70 | 0.8052 |

**Abbreviation**: [a]SD, standard deviation.

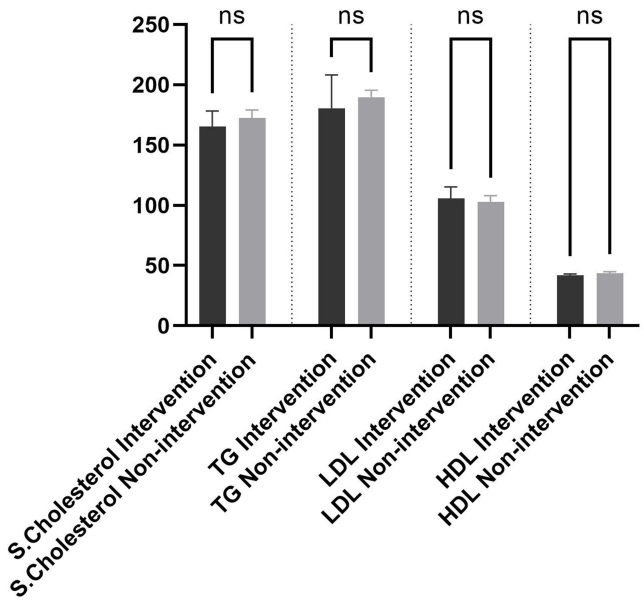


**Figure 14** Lipid profile in intervention and non-intervention group.
**Abbreviations**: s.cholesterol, serum cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ns, non-significance.

risk for DTPs[22,23] and pharmacists are capable of helping patients to overcome the challenges of medication use with chronic diseases.[24]

The data revealed that, out of 322 DTPs on the first visit, the categories of drug therapy problems were sharing inequal numbers. For example, problems related to the indication were taking 38% of total DTPs. While effectiveness, compliance, and safety shares were 34%, 18%, and 7%, respectively. These results are in contrast with previous studies in which most of the DTPs were ascribed to patients' non-compliance towards medications.[25] Two points are emerging here, firstly, the lack of a unified insulin regimen, and secondly, underrating the problems related to indication and effectiveness categories hurdle the patients to achieving a desired therapeutic outcome.

Based on our results, the rate of DTPs is higher (4.67± 1.78 DTPs/patient as mentioned in Table 3) in comparison with other published studies performed by Ogbonna et al, and Koyra et al[22,23] Arguably, this might be amounted to the fact that all of our patients were on insulin, while the number of insulin users were much lower in the above-mentioned articles (17.1% and 27.8% respectively). Despite a high rate of DTPs/patients in both Groups (4.10 ± 1.6 for non-intervention Group and 5.31 ± 1.8 for the intervention Group), a significant reduction (P value< 0.0001****) of DTPs can be seen in the intervention group (from 170 DTPs to 67 DTPs), while the change was insignificant in the non-intervention group (the mean of DTPs/patients were 4.10 ±1.6, 5.1±2, and 4.5 ±1.8, during the 1st, 2nd and 3rd, consequently as shown in Figure 9).

Our data indicated that during the first visit, the most frequently encountered DTP in the intervention group was located in the category of effectiveness with 61 DTPs (36%) followed by Indication with 53 DTPs (31%), compliance with 42 DTPs (25%) and safety with 14 DTPs (8%) as shown in Figure 3. Meanwhile, the most frequently encountered DTP in the non-intervention group was ascribed to the category of indication with 70 DTPs (46%) followed by effectiveness with 49 DTPs (32%), safety with 17 DTPs (11%), and compliance with 16 DTPs (11%) as shown in

**Table 3** Number of DTPs at First Visit

| Groups | Non-Intervention (Mean ± SD[a]) | Intervention |
|---|---|---|
| Average DTPs[b] | 4.10 ± 1.6 | 5.31 ± 1.8 |
| Average DTPs in both groups | | 4.67± 1.78 |

**Abbreviations**: [a]SD, standard deviation; [b]DTPs, drug therapy problems.

Figure 6. After 6 months of pharmacist's intervention, the number of DTPs were significantly reduced among patients in the intervention group, the mean DTPs/patients were 5.3 ±1.8, 3.6±1.9 and 2.2 ±1.8 during the 1st, 2nd and 3rd, respectively. The maximum reduction was noticed in the category of effectiveness where 61 problems were reduced into 11 DTPs towards the end of the study. This was followed by compliance in which out of 42 DTPs in first visit only 15 DTPs were remained at the end of our study, as shown in Figures 3 and 5.

As a consequence of DTP resolution and insulin staging application and providing appropriate pharmaceutical service, we have observed a significant changes in the glycemic picture of patients in both glycated hemoglobin ($p$=0.0001***) (as shown in Figure 10) and fasting plasma glucose (p=0.0032**) (as shown in Figure 11). Meanwhile, our data revealed a non-significant change in the same parameters among patients in the non-intervention group ($p > 0.05$) as presented in Figures 12 and 13. The rate of glycated hemoglobin reduction in our study (>2%) is significantly higher than those studies applying staged diabetes management program alone without pharmaceutical care process. For instance, a prospective, randomized controlled study, of one years' duration performed by general practitioners in France resulted in glycated hemoglobin reduction only by 0.31% in the intervention group.[26]

It is worth to mention that the same clinical outcomes have not been observed in terms of lipid profile (as shown in Figure 14). The issue standing here is that the lipid profile was not high at the baseline for both groups and eighty one percent of the patients were on lipid lowering agents. Despite significant reduction in HbA1c level, there is no significant changes in BW and BMI as presented Table 2. This is in line with the results of a study conducted by Kim et al, in which intensive insulin regimen led to HbA1c reduction significantly without a significant change in BW and BMI.[27]

## Conclusion

Our findings highlight that using of insulin staging therapy in the context of pharmaceutical care process is a promising approach. Detection, prevention, and resolution of DTPs alongside with applying a unified insulin regimen will lead to a significant reduction of plasma glucose levels in patients with T2DM. We have also concluded that clinical pharmacists, as health care providers, can play a pivotal role in applying this unified approach of insulin therapy which in turn leads to a substantial achievement in terms of therapeutic outcomes.

## Abbreviations

T2DM, type two diabetes mellitus; DTP, drug therapy problems; DM, diabetes mellitus; FPG, fasting plasma glucose; $HbA_1c$, glycated hemoglobin; TC, total cholesterol; LDL, low-density lipoprotein; HDL-c, high-density lipoprotein; VLDL, very low-density lipoprotein; TG, triglyceride; BMI, body mass index.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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