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Original Research Article

Anti-diabetic drug utilization patterns in a government hospital in Saudi Arabia

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Abstract

Purpose: *To evaluate the prescription patterns of anti-diabetic drugs in a government hospital in Saudi Arabia.*
Methods: *Retrospective prescription information and medical records of patients who visited outpatient clinics during the last one year were used. The prescriptions were grouped into three: appropriate, partially appropriate and inappropriate. A total of 504 prescriptions were evaluated, while the male to female ratio was 3:1.*
Results: *The mean anti-diabetic drug per prescription was 2.08 ± 0.85. The most common prescriptions were metformin, sulfonylurea and insulin. More than two-thirds of the patients were on combination therapy. No prescriptions were found for thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues and α-glucosidase inhibitors. Metformin/sulfonylurea was the most common combination. The patients that received insulin with an oral agent accounted for 8 % of the total prescriptions. While 62 % of the patients reached fasting blood glucose goal of ≤ 126 mg/dl, there was no correlation between normoglycemia and total number of drugs, gender or age group. Moreover, age, sex, initial glucose concentration, and total drugs had no effect on final glucose levels.*
Conclusion: *Prescription patterns of anti-diabetic drugs are in accordance with international guidelines but some shortcomings were observed probably due to poor prescription writing.*

Keywords: *Diabetes mellitus, Pharmacoepidemiology, Metformin, Interventions, Prescription*

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INTRODUCTION

The World Health Organization (WHO) defined drug utilization studies as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resultant medical, social and economic consequences [1]. The studies are meant to ascertain whether the patterns of prescription, dispensing and usage of medicines are valid and reliable relative to standard guidelines. Besides being a measuring tool for assessment of the outcome of any therapeutic intervention, the WHO has emphasized the use of drug utilization studies as a management tool in healthcare infrastructure planning [2]. Some of the benefits of these

studies include conception and generation of comprehensive medico-socio-economic background data to help in healthcare decision-making [3], rationalization of therapeutic management, identification and formulation of measures to prevent unwanted drug interactions, side effects and toxicity; provision of scientific and evidence-based feedbacks to physicians, pharmacists and other stakeholders; and generation of conceptual framework in the implementation of learning programs ultimately leading to improvement in prescription practices [1].

Incongruous drug use patterns such as irrational prescriptions, unnecessary multi-drug regimens and disproportionate doses, reduce the effectiveness of drug therapy, causing non-adherence, escalating the incidence of adverse drug reaction (ADR) and amplifying the cost of medical care [4]. Therefore, it is imperative to evaluate the prescription patterns periodically so as to detect shortcomings and immediately embark on effective corrective measures.

Diabetes mellitus is a chronic disorder characterized by hyperglycemia and insulin resistance associated with metabolic irregularities related to carbohydrate, protein and fat metabolism [5]. In 2000, there were about 171 million reported cases of diabetes worldwide. This number is rapidly increasing and may reach 366 million by 2030. The Kingdom of Saudi Arabia (KSA) is one of the countries witnessing acute rises in diabetic cases. According to global data, the estimated prevalence was about 20 % in 2007 and the deaths due to diabetes and its complications were more than one-tenth (10 - 14 %) of all the deaths that occurred in persons aged between twenty and seventy nine years.

Chronic uncontrolled diabetes leads to micro- and macro-vascular complications such as neuropathy, nephropathy and retinopathy, which severely affects productive life, decreases quality-adjusted life years (QALYs) and increases economic healthcare burden. It is one of the leading causes of renal failure, blindness and amputation especially in developed nations [6]. Thus, diabetes mellitus has biological and economic impacts on health [7]. Major pharmacological management guidelines for diabetes include the use of injectables such as insulin, GLP-1 receptor agonists and oral hypoglycemic agents like biguanides, sulfonylurea, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors [8].The aim of this study was to evaluate the prescription patterns of anti-diabetic drugs in a government hospital in the KSA, and to determine whether the patterns were in accordance with international guidelines. The relationship between these patterns and attainment of normoglycemia was also investigated.

METHODS

Study design

Retrospective prescription information from medical records of diabetic patients was used in this study. A total of 504 prescriptions were analyzed. The mean age of the patients was 52.87 ± 12.53 years. There were 384 males (76.20 %) and 120 females (23.80 %). All outpatient prescriptions from within the hospital received and maintained in the pharmacy were studied, irrespective of the clinic of origin. Demographic data and blood glucose concentrations were recorded. Details such as brand/generic name, indication, route of administration, dose, frequency, and duration of each drug prescribed were recorded. The prescriptions were examined for order, number and therapeutic class of the drugs and appropriateness.

Percentages of different classes of drugs prescribed for the patients were also documented. The prescriptions were grouped as (a) "appropriate" when the drugs prescribed were fully related to the diagnosis, (b) "partially appropriate" when the drugs were partially related to the diagnosis, (c) "inappropriate" when no relationship existed between the drugs prescribed and the diagnosis and/or when it was difficult to comment due to missed diagnosis and/or unclear writing [7]. Assessment of deviations from the guidelines was done according to criteria of guidelines for the diagnosis and management of diabetes [8]. Minor and major deviations were conferred with one drug only, and two or more drugs, respectively. Ethical approval (No. A00230) was obtained from the Directorate of Health Affairs, Jeddah Ministry of Health, Saudi Arabia. The study was conducted according to the international ethical guidelines for health-related research involving humans [9].

Population and sample size

Medical records of patients, attending the outpatient clinics were scanned by systematic random sampling. The sample size was calculated using the following formula:

$Z_{1-\alpha/2}^2(SD)^2/d^2$

where $Z_{1-\alpha/2}$ is the standard normal variate (1.96 at 5 % type I error), SD is the standard deviation from previous (pilot) studies; and 'd' is the precision error which was set at 5 %.

Statistical analysis

Data were analysed using SPSS (version17.0). Descriptive analysis was used for all variables. Correlation and regression analyses were performed to test the relationship between variables and to see if the variables had effects on glycemic control. Data are presented as mean ± SD. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Age group distribution of patients

Demographic pattern of the study population is shown in Table 1. Most cases were within the age range of 45 – 60, while others were within 30 - 45 years.

Table 1: Demographic characteristics of the study population

Age group (years)	Sex		Total
	Male (%)	*Female (%)*	*Total*
< 30	8* (1.60†)	0 (0.00)	8 (1.60)
30 – 45	120 (23.80)	40 (7.90)	160 (31.70)
46 – 60	160 (31.70)	32 (6.40)	192 (38.10)
> 60	96 (19.00)	48 (9.60)	144 (28.60)
Total	384 (76.20)	120 (23.80)	504 (100.0)

*Denotes absolute number; †denotes frequency

Pattern of anti-diabetic drug intake of patients

Majority of the patients were taking at least two drugs (48.20 %), while 19.10 % of the patients were on triple therapy. Thus, over 67 % of the patients were on combination therapy (Figure 1). A detailed pattern of drug consumption across different age groups and sex is shown in Table 2.

Patients within the age range of 45 - 60 years on mono- or combination therapy had maximum percentage of drug utilization. However, across all age groups the percentages of male and female patients on triple drugs were almost at par (9.50 %). The dual therapy included a combination of metformin and one sulfonylurea drug, combination of metformin and insulin, and combination of metformin and gliptins. Triple therapy consisted mainly of combination of metformin, sulfonylurea and insulin, and combination of metformin, sulfonylurea and gliptins/SGLT-2 inhibitors.

The most common oral anti-diabetic drug prescribed alone or in combination was metformin (36.29 %) followed by gliclazide (11.97 %) from the sulfonylurea group. The overall combined percentage of sulfonylurea prescription was about 30.68 %. Approximately 27.30 % of the patients were prescribed insulin, either alone or in combination with other drugs.

Patients who were on a combination of insulin and an oral anti-diabetic drug comprised 8 %, and the most common oral drug combined with insulin was metformin. More than 65 % of the patients were on insulin. The insulin administered was premixed 30/70. The most common type of premixed was Novomix 30® containing a combination of 30 % soluble insulin aspart (rapid-acting) and 70 % protamine-crystallized insulin aspart (intermediate-acting); followed by Humulin 30/70® containing a combination of regular (30 %) and 70 % human insulin isophane (NPH). A few patients were prescribed short- or long-acting insulin singly. Newer drugs like DPP-4 and SGLT-2 inhibitors also had a niche, being prescribed to a total of 3.74 and 2.01 %, respectively. However, there was no record of GLP-1 agonists such as exenatide and liraglutide, thiazolidinediones, and α-glucosidase inhibitors. All the drugs were from essential medicine list, except canagliflozin and vidagliptin.

The mean number of drugs across different age groups was 2.08 ± 0.85; it did not increase significantly ($p > 0.05$) with age.

Table 2: Total number of drugs distributed across age groups and sex

Age group (years)	Total number of drugs						
	01		02		03		
	M	**F**	**M**	**F**	**M**	**F**	**Total**
< 30	1.00	00	0.60	00	00	00	1.60
30- 44	7.90	00	12.70	3.20	3.20	4.70	31.70
45- 60	11.10*	3.20	15.80*	1.60	4.80*	1.60	38.10
> 60	6.30	3.20	11.10	3.20	1.60	3.20	28.60
Total	26.30	6.40	40.20	8.00	9.60†	9.50†	100.00

*Maximum percentage; †equal or no difference in percentage of patients

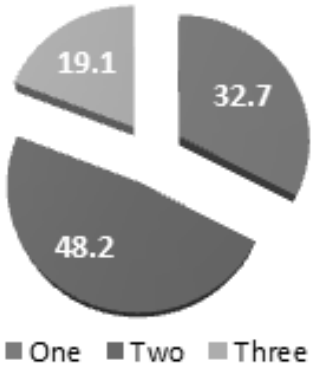

Figure 1: Percentage of patients for whom anti-diabetic drugs were prescribed. Majority of the patients (48.20 %) were on at least two drugs, while 19.10 % patients were on triple therapy. Thus, more than 67 % of the patients were on combination therapy

There was no significant correlation between age groups and number of drugs (R = - 0.1, *p* = 0.379). The most common co-morbidities were hypertension (28.3 %), dyslipidemia (19.40 %), obesity (13.70 %) and a previous cardiovascular event (9.60 %).

The initial fasting plasma glucose (FPG) was 211.32 ± 87.77 mg/dL. Post-treatment FPG (last reading during the study period) was 125.19 ± 18.19 mg/dL. Data on post-prandial glucose and glycated hemoglobin (HbA1c) concentrations were missing from many files. About 61.90 % of the patients reached the FPG goal of ≤ 126 mg/dL, and out of this, a slightly higher percentage of females (66.70 %) reached the goal than males (60.41 %), but the difference was not significant (*p* = 0.453).

A greater percentage of patients on monotherapy reached the goal (75 %) than those on combination therapy (60 %). However, there was no correlation between patients reaching the goal and total number of drugs (R = -.02, *p* = 0.857), or between patients reaching the goal and age groups (R = 0.11, *p* = 0.388), respectively.

Multiple linear regression analysis of variables affecting post-treatment FPG

As shown in Table 3, linear regression was performed to see if age, age group, sex, initial FPG concentration, and total number of drugs had effect on final FBG concentration. The results showed that the final FPG was not affected by any of these variables.

About 83.70 % of the prescriptions were appropriate, 7.90 % were partially inappropriate, and the rest (8.40 %) were inappropriate. Generally, the prescription patterns were in accordance with international guidelines, but some shortcomings were observed probably due to poor prescription writing.

Table 3: Possible effects of variables on fasting plasma glucose values (last) by linear regression model

R^2=-0.047; F=0.457, p=0.807		
Variable	**β***	***P-value***
FPG (initial recorded)	- 0.022	0.883
Age	- 0.369	0.378
Sex	0.092	0.507
Total number of drugs	- 0.118	0.407
Age group	0.197	0.622

β= standardized coefficient, FPG = fasting plasma glucose*

DISCUSSION

The present study was carried out to evaluate the prescription pattern of anti-diabetic drugs in a government hospital in Saudi Arabia. The results showed that there were more males with diabetes than females. This observation is in agreement with a previous study carried out in Saudi Arabia [10], suggesting a possible role of estrogen in protecting women against insulin resistance [11]. Majority of the patients were on combination therapy, which is in agreement with previous studies [12,13]. This may be partly attributed to failure to achieve normoglycemia with one medication. Recent guidelines encouraged the use of combination therapy from the outset if HbA1c is high, and when patients fail to attain normoglycemia after a certain period. The current guidelines of the American Association of Clinical Endocrinologist/American College of Endocrinology (AACE/ACE) advocate the use of dual therapy in patients with initial HbA1c levels > 7.50 %, and dual/triple combination therapy in patients with initial HbA1c levels > 9.0 % in addition to asymptomatic hyperglycemia [8]. The American Diabetes Association (ADA) also endorsed dual therapy in cases where HbA1c > 9.0 % or where there is failure to achieve treatment target within three months. Thus, combination therapy is considered optimal for many patients.

In the present study, male patients of age range 45 to 60 years formed the largest drug utilizing group. However, when analyzed across all age groups, the percentages of male and female patients consuming triple drugs were almost at par. These results appear to suggest that sex may play a role in the initial response of patients to therapy as evident in the percentage differences between males and females when the patients were on single/dual therapy. However, as the disease progresses, this

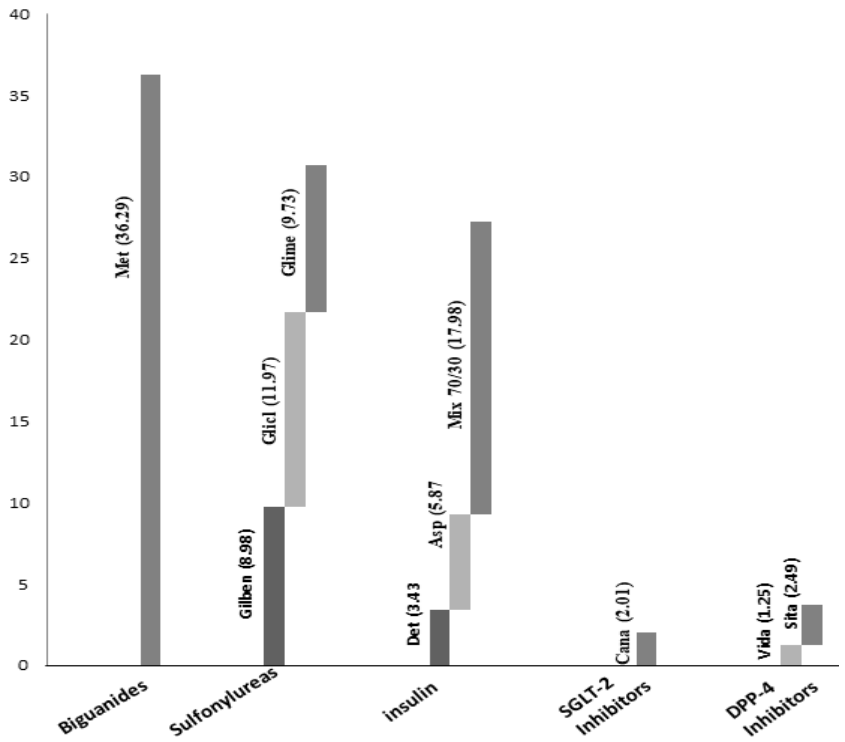

Figure 2: Prescription pattern of anti-diabetic drugs. The most common oral drug prescribed alone or in combination was metformin (36.29 %), followed by gliclazide (11.97 %) from sulfonylurea group. Overall combined prescription of sulfonylurea was 30.68 %. Approximately 27.30 % of the patients were on insulin, either alone or in a combination. Met = metformin, Gilben = gilbenclamide, Glicl = gliclazide, Glime = glimepiride, Det = deterimer, Asp = aspart, Premixed = mixture of 30/70, Cana = canagliflozin, SGLT-2 = sodium- glucose co-transporter-2, DPP- 4 = dipeptidyl peptidase - 4, Vida = vidagliptin, Sita = sitagliptin

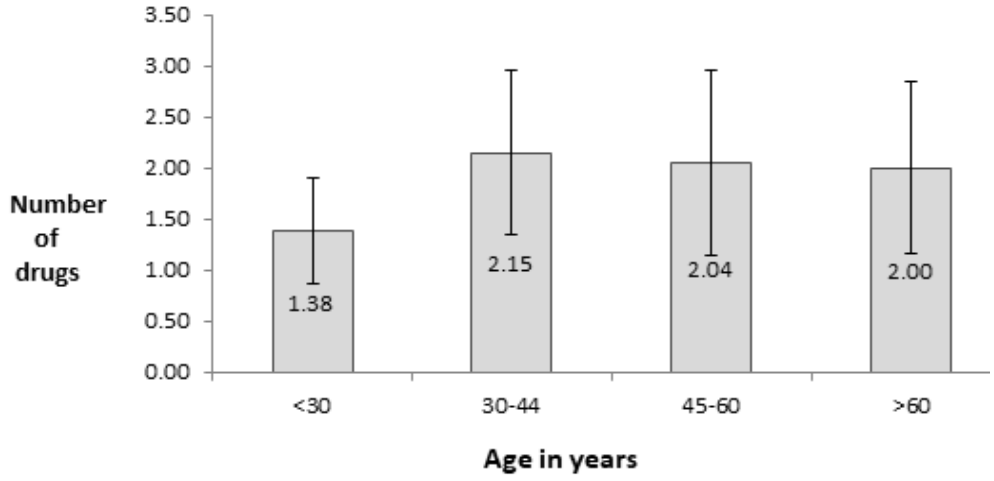

Figure 3: Mean number of drugs prescribed across different age groups. The overall mean (2.08 ± 0.85) did not increase significantly with age ($p > 0.05$). Moreover, there was no significant correlation between age groups and number of drugs

protective effect may be lost [11]. The most common combination was metformin + sulfonylurea (SU). A previous study from India also reported the use of the combination of metformin with a different SU by a large number of diabetic patients [14]. Metformin has beneficial effects on insulin resistance, while SU helps to prevent insulin deficiency by stimulating its release by the pancreatic β-cells. The next most common combination was insulin with an oral agent, either metformin or sulfonylurea. A previous study showed that the combination of insulin and metformin is more effective for achieving normoglycemia than insulin monotherapy or a combination of insulin and sulfonylurea [15]. Combination of insulin and SU

has been used in the past and was known as bedtime insulin and daytime SU (BIDS) therapy. It has been speculated that insulin spares the effect of SU, bringing about a 30 % reduction in daily insulin dose, less weight gain, and less incidence of hypoglycemia [16]. However, some studies advocated that because of similarities in the actions of insulin and SU, normoglycemia can be achieved with insulin alone at a slightly higher dose [17].

In the present study, the percentage of patients on triple combination therapy was low. Recent AACE guidelines have recommended triple therapy either from the start in some cases, or quick progression to triple therapy depending on the patient's condition, compliance and disease progression. If the dual therapy of metformin + SU fails to achieve HbA1c goal, then insulin should be added gradually until SU is finally discontinued. A study by Rosenstock *et al* reported a 1.5 % reduction in HbA1c after 24 weeks of treatment with metformin + SGLT2 + DPP-4 without any side effects [18]. Another recommended option is metformin + SU + DPP-4/SGLT-2 or metformin + SU + GLP-1 especially in patients at risk of hypoglycemia and weight gain. It has been reported that addition of insulin to the prescription of a patient who fails on a dual therapy is better than addition of a third oral agent, in view of the safety profiles and side effects of individual drugs [19]. However, the incidence of hypoglycemia must be taken into consideration while adding insulin instead of a third oral drug.

In this study, metformin was the most common oral agent, with sulfonylurea next in ranking. This finding is in agreement with results from previous studies [10,14,20], although individual sulfonylurea drug utilization pattern was different. It has been reported that SU is used to a greater extent than metformin [21]. Metformin primarily reduces hepatic gluconeogenesis, increases peripheral insulin sensitivity, and causes less intestinal glucose absorption. It is often the preferred first line oral therapy especially for obese patients unless contra-indicated. The pattern of use of metformin is probably due to its effectiveness, safety profile, role in weight loss, and less danger of hypoglycemia. The findings from this study are in agreement with established guidelines.

Data for insulin use as mono- or combination therapy in this study were in agreement with data from a previous study [22]. Some patients with progressive diabetes may need to switch to insulin early. Recent guidelines also provide that if a patient is not treated with two oral agents, then insulin must be considered. However, disease state, complications, age, and compliance issues must be taken into consideration. In the present study, premixed insulin was most frequently prescribed. Newer drugs like DPP- 4 and SGLT- 2 inhibitors were also prescribed, but to a lesser extent. The SGLT- 2 inhibitors block proximal reabsorption of glucose and increase renal glucose excretion. They also protect against hypertension, obesity and insulin resistance. Their effectiveness is well documented in the literature, but due to high renal glycosuria, they may predispose to renal infections and dehydration. The Food and Drug Administration of the US (FDA) has warned that SGLT-2 inhibitors can predispose to diabetic ketoacidosis, especially in patients undergoing surgery or with low beta-cell reserve.

Incretin-based therapies mainly consisted of DPP-4 inhibitors and GLP-1 receptor agonists. However, no prescriptions were found for GLP-1. Sitagliptin and vildagliptin (DPP-4 inhibitors) have similar effectiveness as metformin in reducing hyperglycemia. Saxagliptin and vidagliptin are able to reduce HbA1c levels after 24 weeks. Inhibitors of DPP-4 have advantages over the GLP-1 analogs especially in renal failure, and in situations when weight loss is not a priority. However, FDA have warned that joint pains are associated with long-term use of DPP-4 inhibitors.

One of the peculiar findings in the present study is the absence of pioglitazone and rosiglitazone in the prescriptions. Previous studies showed that some patients are still been prescribed these medications [10,12,14]. However, after recent reports on the safety of these medications, their use have dramatically decreased globally [23]. The mean drug per prescription was lower when compared with a previous study [16], but slightly higher than that reported in a study conducted in India [24].

The last recorded post-treatment fasting plasma glucose (FPG) showed that patients responded to the treatment, but they fell short of mark by not reaching the desired glycemic goal. In this study, a higher percentage of patients on monotherapy were able to reach the goal (although not statistically significant) when compared to combination therapy. A similar observation was reported in a previous study [25]. This may be due to the presence of co-morbidities, advanced state of disease, compliance or adherence issues, and drug interactions. The variables had no effect on plasma glucose concentration, but important data like postprandial glucose concentrations, HbA1c, body mass index (BMI),

adherence scores, and treatments for co-morbidities need to be considered before a categorical and conclusive statement is made. However, these results highlight the importance of individualized therapy.

Limitations of the study

The likely limitations of this study include the use of a single health facility, failure to study some prescriptions due to missing diagnosis and illegible writing, and inability to have a follow-up.

CONCLUSION

In general, the results obtained in this study indicate that the prescription patterns of anti-diabetic drugs are in accordance with international guidelines. However, some shortcomings do exist, probably due to poor prescription writing.

DECLARATIONS

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Conflict of interest

The authors declare that no conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. MMR and HAM conceived and designed the study, ZJG and ZMS collected and analysed the data, MMR and HAM wrote the manuscript, and all authors read and approved the manuscript.

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