

DRUG USE EVALUATION OF DIABETES MELLITUS IN NON-HOSPITALIZED PATIENTS

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Received: 10 May 2016 Revised and Accepted: 20 Jun 2016

ABSTRACT

Objective: As irrational drug administration in these patients can increase the overall burden of Diabetes Mellitus (DM) on the health system in different societies, we decided to investigate the patterns of antidiabetic drug administration and the way these patients are monitored in our community.

Methods: This is a prospective cross-sectional study performed in the city of Zabol in a 9 mo period. Diabetic patients, who referred to local pharmacies, were interviewed and data about their demographic characteristics, current and previous anti diabetic regimen, adverse drug reactions co morbidities as well as diabetes symptoms on diagnoses and its complications were collected.

Results: Our study showed that metformin was the most frequent used oral hypoglycemic agents (OHA) (66.4 %) followed by sulfonylurea, and the most prevalent combination therapy was metformin/glibenclamide regimen (28.5%). The majority of patients treated with metformin at the time when they were diagnosed with diabetes (45.3 %). In terms of co-existing disease and target organ damages, hypertension and visual impairment ranked first in our study population. Hypoglycemic episodes were most commonly reported adverse events with insulin and gastric upset with OHAs. 60.3% of our patients didn't follow regular blood glucose checkup.

Conclusion: It is concluded that the prescribing pattern in DM is moving from monotherapy with either insulin or sulfonylureas towards combination therapies. This study strongly highlights the need for patient education and comprehensive counseling about the importance of strict commitment to antidiabetic regimen, lifestyle modification, monitoring blood glucose as well as its related complications regularly, for successful management of diabetes.

Keywords: Diabetes Mellitus, Drug Use Evaluation, Anti Diabetic Drugs

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INTRODUCTION

Drug administration is a complex process, on one hand medication has saved thousands of lives all around the world on the other hand inappropriate drug use may also cause several problems as; increased treatment cost, antimicrobial resistance, adverse drug reactions and even death. Hence, in recent years, drug use evaluation studies have become a potent tool to evaluate the health system efficacy and safety [1].

Drug use evaluation (DUE) is a performance improvement method that focuses on evaluation and improvement of drug use processes to achieve optimal patient outcomes based on a systematic evaluation of drug use. DUE may be applied to a drug therapeutic class, disease state or condition as well as a drug use process or outcomes. The total process of medication prescribing, from ordering a drug by doctors, to administration by nurses, could be assessed by DUEs. It is not only a process to identify drug use problems, but also can provide a means to correct the problems and contribute to rational drug therapy [2].

Diabetes mellitus (DM) is a chronic metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both [3]. It is currently estimated that 382 million people all around the world suffer from DM, with over 592 million predicted to suffer this condition by 2035, according to the International Diabetes Federation (IDF) report [4]. The prevalence of diabetes in Iran in 2013 was 8.4% (4.395 million people) in the IDF Diabetes Atlas and estimated to grow to 12.3% (8.396) by 2035 with 2.198 million unknown cases [5]. It is estimated that 90-95% of all diabetic patients have type 2 diabetes, while 5-10% have type 1 diabetes [4-8]. Chronic hyperglycemia in diabetes will damage, various organs, especially the eyes, kidneys, nerves, heart and blood vessels [3]. In most cases, diabetes coexists with hypertension and dyslipidemia [5, 8]. So management of diabetes is an important

international issue that can be roughly categorized in three major components: diet, drugs (insulin and oral hypoglycemic agents), and exercise [6]. Today various drugs are available for the treatment of diabetes mellitus that can be used as a mono or combination therapy [4]. Although there are several established guidelines on the treatment of diabetes, but the preferred therapeutic regimen varies all over the world [7].

Considering the growing rate of DM [5], frequent use not recommended combination therapies, high incidence of its micro and macro vascular complications [8, 9] and patients unaware of the progressive nature of this disease, justifies the evaluation of drug use pattern and its related problems in diabetic patients to improve clinical outcomes and quality of life of these patients [1]. As we did not have any reliable data about diabetes in our community, we carried on a medicine utilization study about anti-diabetic agents in non-hospitalized patients referring to local pharmacies. The main aim of our study was to describe the patterns of medication prescribed and monitoring parameters performed, in an outpatient setting, to formulate comprehensive guidelines for better management of our diabetic patients.

MATERIALS AND METHODS

Methods

Our prospective, cross-sectional study was carried out in the Zabol city, Sistan and Bluchestan province, Iran, in a 9 mo period (May 2011–March 2012) after obtaining research and ethical approval from the Zabol University of Medical Sciences. Prescriptions of patients referring to local pharmacies were reviewed by the interviewer when they addressed pharmacies to collect their medications. Prescriptions containing at least one anti diabetic agent either insulin or oral hypoglycemic agent (OHA) were selected, then patients were asked to enter the inner part of the pharmacy for interview. After explaining the aim of the study for the patient and

obtaining verbal informed consent, required questions were asked of the patient and relevant data were extracted from patient prescription. These data were used to complete our predesigned data collection forms. Following information was included in our checklist:

A: Patient demographic details: age, gender, history of cigarette smoking, detailed past medical and drug history, family history of diabetes and the time period has been diagnosed with diabetes.

B: Information about diabetes management: Doctor specialty, number of drugs in current prescription, current and previous anti diabetic regimen, any side effects experienced by the patient, administration of any herbal or home remedies and if current drug regimen was different from previous regimen and the reason for this substitution.

C: Target organ damage: retinopathy, nephropathy, neuropathy and diabetic foot.

D: Patients' symptoms when diagnosed with diabetes: fatigue, weight gain, weight loss, recurrent vaginal candidiasis, numbness and tingling in extremities, polyuria, polydipsia, increase appetite.

E: Intervals between blood sugar monitoring tests and commitment to any medical life style management recommendations.

After completing checklists, they were analyzed for various parameters included, performing descriptive statistical analyses using SPSS version 20. Descriptive statistics for continuous variables were expressed as means and standard deviation (SD). The differences in proportions were compared by unpaired t-test where appropriate. Statistical significance was set for $p < 0.05$.

RESULTS

During the study period, a total of 267 patients aged from 15-85 y old, were interviewed, that 116 (43.4 %) cases were male and 151 (56.5 %) were female ($P < 0.05$). A large number of our study population (32.5%) was between 50 to 59 y old, with a mean age of 55.22 ± 12.72 y (fig. 1). Positive family history of diabetes was reported in 116 (43.4 %) patients. A high percentage (67%) of our diabetic patients was found to be comorbid ($P < 0.0001$, extremely significant) with different types of diseases; as hypertension in 136

(50.9 %) patients, followed by hyperlipidemia in 117 (43.8%) cases and, other cardiovascular diseases (17.9%).

About 75 (28.1%) patients reported at least one end organ damage; visual impairment (retinopathy) was most frequently reported complication (fig. 2).

Among the study population, 125 (46.8%) patients have been diagnosed with diabetes for less than 5 y, followed by 5-10 y positive history in 78 (29.2%) patients. The rest of them (23.9%) had suffered from diabetes for more than 10 y, and the mean duration of being diagnosed with diabetes, was 6.62 ± 5.81 y. The most common reported symptom at the time they were diagnosed with diabetes, was polyuria (66.7%) followed by polydipsia (61.8%) and fatigue (57.6%).

Diabetes management

Medical nutrition therapy and physical activity

Only 9.7% of these patients reported to have regular physical activity for at least 30 min/day and rest of them had irregular or no physical activity. Most popular physical activity among them was walking (96.5%). In terms of medical nutrition therapy, 46.1% of patients claimed to follow some sort of self-planned diet, but no one had a history of visiting a nutritionist.

Using alternative medicine

The majority of patients (95.5%) were not on any alternative medication, but 4.5% of patients reported using different types of medicinal herb, besides their pharmacological therapy as follows: green tea, sore tea, apple vinegar, cinnamon, lavender, bitter cucumber and dill.

Drug regimen

Metformin was the most prescribed OHA prescribed at the time of diagnoses of diabetes, in our study population, most commonly as monotherapy. It was used as combination therapy with glibenclamide less frequently (table 1). To look at different pharmacological classes of OHA, biguanides ($n = 160$, 37%) were the most commonly prescribed drug class, followed by sulfonylureas ($n = 138$, 31.9%), thiazolidinediones ($n = 107$, 24.8%) and alpha-glucosidase inhibitors ($n = 27$, 6.3%).

Table 1: Prescribed antidiabetic regimen at the time of diabetes diagnosis

Type of drug regimen	Drug name(s)	No. of prescriptions (%)
Monotherapy	Insulin	16 (5.9)
	Metformin	121 (45.3)
	Glibenclamide	70 (26.2)
	Gliclazide	7 (2.6)
2-drug therapy	Metformin+Glibenclamide	49 (18.3)
	Metformin+Gliclazide	4 (1.5)
Total		267 (100%)

Metformin was also the most common drug prescribed in their current antidiabetic regimen followed by sulfonylureas and insulin (table 2). Combination therapies were prescribed in 52.4% of patients, as metformin+glibenclamide and metformin+glibenclamide+pioglitazone

as the most prevalent 2 and 3 drug combination regimen. Other prescribed regimens are described in table 3. More patients received combination therapy ($n = 143$, 71.5%) compared to monotherapy ($n = 57$, 28.5%), $P < 0.0001$.

Table 2: Current anti diabetic drugs prescribed in our study population

Drug class	Drug name	Number of prescription (%)
Insulin	Regular	42 (15.7)
	NPH	45 (16.8)
	Glargine	14 (5.2)
	Aspart	9 (3.3)
Biguanide	Metformin	172 (64.4)
Sulfonylureas	Glibenclamide	132 (49.4)
	Gliclazide	20 (7.4)
Thiazolidinediones	Pioglitazone	21 (7.8)
Alpha glucosidase inhibitors	Acarbose	14 (5.2)

Table 3: Current antidiabetic regimens used in our study population

Type of drug regimen	Drug name (s)	Number of prescription (%)
Monotherapy	Insulin	43 (16.1)
	Metformin	54 (20.2)
	Glibenclamide	26 (9.7)
2-drug therapy	Gliclaside	4 (1.5)
	Insulin+Metformin	11 (4.1)
	Insulin+Glibenclamide	1 (0.3)
	Metformin+Glibenclamide	76 (28.4)
	Metformin+Gliclaside	14 (5.2)
	Metformin+pioglitazone	6 (2.2)
	Glibenclamide+Acarbose	4 (1.5)
	Glibenclamide+pioglitazone	4 (1.5)
3-drug therapy	Gliclaside+Acarbose	1 (0.3)
	Insulin+Metformin+Glibenclamide	4 (1.5)
	Insulin+Metformin+Acarbose	1 (0.3%)
	Insulin+Glibenclamide+Acarbose	1 (0.3%)
	Metformin+Glibenclamide+Acarbose	5 (1.8%)
	Metformin+Glibenclamide+pioglitazone	9 (3.3%)
4-drug therapy	Metformin+Gliclaside+pioglitazone	1 (0.3%)
	Insulin+Metformin+Glibenclamide+Acarbose	1 (0.3%)
	Metformin+Glibenclamide+pioglitazone+Acarbose	1 (0.3%)
		2 (0.7%)
Total		267 (100%)

Common reported side effects

Hypoglycemia was the most commonly reported side effect with insulin (17.2%). Loss of appetite was most frequently reported with OHA (5.9%) followed by nausea (5.2%) and dyspepsia (4.76%).

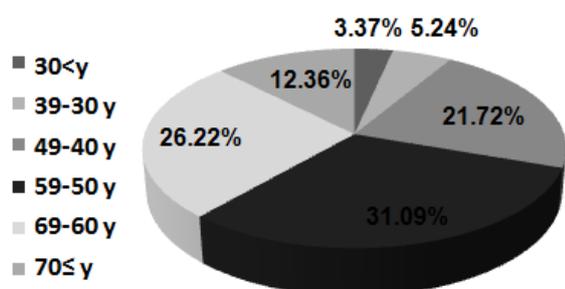


Fig. 1: Age distribution of patients

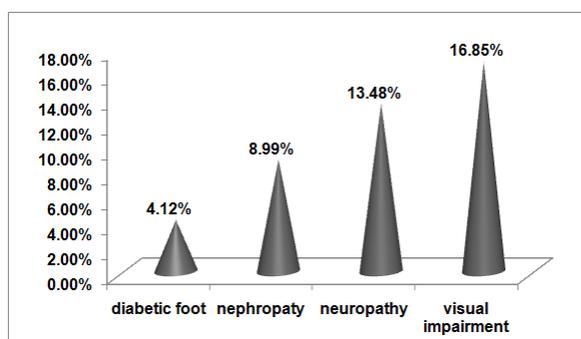


Fig. 2: Distribution of diabetic complications

Co-medications

Our results showed that 143 (53.5%) patients from our study population received at least one cardiovascular drug besides their anti-diabetic regimen. Among them statins were the most prevalent prescribed drugs (33.7%) and beta blockers and angiotensin receptor blockers (ARBs) ranked second and third with 23.2% and

22.5% rates respectively. Metoprolol and atorvastatin were the most frequently prescribed beta blockers and statins, while among ARBs and angiotensin converting enzyme inhibitors (ACEIs), losartan (20.6%) and captopril (8.6%) were prescribed more frequently.

Monitoring of blood glucose

Only 27 (10.1%) patients claimed that they had regular daily blood glucose monitoring who were all on insulin therapy. Unfortunately the majority of patients (60.3%) reported that they monitor their blood glucose level once per month or less frequently.

DISCUSSION

Our study showed, that unfortunately diabetic patients are not monitored properly in our community and the majority of these patients are not appointed to regular doctor visits and do not follow any American Diabetes Association (ADA) recommendations on blood glucose monitoring, diet or physical activity. We also concluded that most of our diabetic patients have a long history of diabetes and are comorbid with diseases like hypertension and dyslipidemia that need to be managed carefully, otherwise would more complicate their outcome.

Our study showed that the majority of our diabetic patients ranged between 50 to 60 y old. While Khamali *et al.*, [1] concluded that diabetes was more frequent in the age group of 60-70 y. The mean±SD age of patients in this study was 55.2±12.7 y, similar to the results from some other studies [10-13], but this value is more than 10 y lower than what reported in some developed countries [14-17]. These results showed that diabetes starts in lower ages in our society that justifies the need for careful screening for diabetes from young ages, especially among patients who have a positive family history and are high risk for cardiovascular diseases.

Our results showed that diabetes is more prevalent in female that was in agreement with the results of other studies [1, 18]. In fact the risk of type 2 diabetes is 1.7 % greater in females compared to males in our country [19]. This may be related to the fact that obesity is more prevalent in Iranian women [20], because they normally have less physical activity compared to men, so weight control programs and following healthy lifestyle modifications are strongly recommended in this population.

In the present study, the mean duration of being diagnosed with diabetes, was 6.6±5.8 y compared to 11.8±8.0 y in a similar study performed in Spain [14]. This may reflect the fact that, we may not be as successful as other countries in early detection of diabetic patients. Considering the fact that patients with prolonged history of

diabetes, like our study population, are at increased risk of developing micro and macro-vascular complications of diabetes [7], the need for more frequent follow up visits and careful monitoring of sign and symptoms of related end organ damages are prudent.

In terms of medical life style modification, we observed that unfortunately the majority of our study population are not adherent to any of the American Diabetes Association (ADA) recommendations about exercise and diet. Studies in other parts of Iran showed that although commitment to a strict diet regimen was not a common approach elsewhere, but people were involved in regular physical activity more frequent [25]. Lack of overall knowledge about the impact of diet and physical activity for achievement to the desired outcome in diabetes management is a major contributor, which justifies investing in better education of both doctors and patients, about this therapeutic modality, and also involving expert nutritionists as a member of diabetic management teams.

The rate of reported adverse drug reactions with OHA and insulin, varies in different studies, but as we observed, almost always the most common side effect reported with metformin is dyspepsia, and hypoglycemia and weight increase with sulfonylurea and thiazolidinedione [26]. Considering the fact that most of these patients take other medications with similar side effects, it would be difficult to differentiate these side effects from each other and even from symptoms related to the subject disease. Totally we did not encounter any serious side effect with these drugs and they were commonly well tolerated. In case of Insulin therapy, the most common adverse effect in our study population was hypoglycemia and the rate of this adverse effect was similar to that reported in other studies [27].

The ADA recommends metformin as the first step in diabetes management [28]. Our results showed that about half of our study population was managed based on this guideline. But we should consider the fact that ADA guideline has not only approved the protocol for diabetes management, and it does not necessarily indicated that the rest of patients are managed inappropriately. For example, in the American Association of Clinical Endocrinologist (AAACE/ACE) Guideline, monotherapy with thiazolidinedione and even combination therapy are mentioned as therapeutic options in the first step of diabetes management [29]. Even in some other guidelines like; Scottish Intercollegiate Guideline Network (SIGN), International Diabetes Federation (IDF) and National Institute for Health and Care Excellence (NICE), sulfonylurea are mentioned as the first therapeutic option, especially for non-obese patients with high blood glucose, who needs a rapid blood glucose reduction [30-32]. To sum up, apart from the guidelines recommendations, the first therapeutic choice in diabetes management, depends on different factors like patients related factors, drug availability and cost and it is better to be individualized [33].

Combination therapy was used more common than monotherapy in our study population. The prevalence of combination therapy reflects the fact that diabetes mellitus is a progressive metabolic disease, which is difficult to be managed appropriately, and the majority of patients with an acceptable initial response to one OHA may eventually require a second or even third medication. On one hand combination therapy may guarantee the best control of blood sugar [34], on the other hand it may increase the risk of drug duplication, drug interactions and adverse drug reactions as well as increase treatment cost [14]. Sulfonylureas remain the best choice to be combined with metformin, although their effectiveness decreases with time [1]. The concurrent use of a sulfonylurea and metformin is synergism because of the insulinogenic effect of the former and the beneficial effects of the latter on insulin resistance. That is why it is still the most recommended and prevalent combination therapy in diabetes [1, 3, 34].

Evaluation of patients current prescription also revealed that metformin (64.4%) was the most common prescribed OHA in our study population, like what was reported in various studies conducted all over the world [3,10-13, 22, 35, 36]. Metformin is recommended by the majority of guidelines [28, 31, 37] due to its efficacy, desirable effects on weight and lipid profile, it's low cost and acceptable adverse effect profile [3]. It also doesn't induce

hypoglycemia and can be used with other antidiabetic agent as combination therapy [1]. It decreases insulin resistance that is a proven risk factor for different cardiovascular disease [3]. It is also proved that metformin can reduce macrovascular complications of diabetes, such as myocardial infarction and stroke [1].

The majority of our sulfonylurea-treated patients like many other similar studies [11, 13, 22, 38], received glibenclamide, probably due to its low cost and prolonged history in clinical practice.

Regarding co-administered drugs, we observed that atorvastatin was administered most frequently in our study population, followed by beta blockers and ACEIs/ARBs. Although ACEIs and ARBs are categorized as antihypertensive drugs, it is worth to notice that they may be prescribed for indications other than hypertension management, in diabetic patients. The fact that beta blockers are not recommended by JNC VIII as first line anti-hypertensive agents [8, 39] besides their potential undesirable effect on blood glucose level (especially non-selective beta blockers) and masking signs and symptoms of hypoglycemia, it is better to be avoided in this population [40]. High prevalence of beta blocker administration, in our study population may reflect the lack of updated knowledge about recent guidelines and recommendation on the management of hypertension and pharmacology of drugs by prescribers.

Limitations

The major limitation of our study is the fact that as we did not have any diabetes clinic at the time of study, we did not have access to any documented data from our patients, as well as their lab results, so we had to rely on subjective data from patients' interview.

CONCLUSION

In conclusion, the results of this study highlight the need for careful management of diabetic patients, including their lifestyle, adherence to drug therapy, diabetes complications and comorbidities through regular follow up visits by a General Practitioner or preferably through establishing a diabetes clinic. Our results also strongly recommend comprehensive patient education programs about different components of diabetes management. Our study also highlights, role of community pharmacists as one of the primary care providers to minimize drug-related problems and therefore promoting patient compliance with the prescribed regimen.

The authors declare that they have no competing interests.

Authors' contribution:

"MM participated in the design of the study, coordinates data collection and drafted the manuscript. SM participated in the design of the study and performed the statistical analysis and helped to draft the manuscript".

CONFLICT OF INTERESTS

Declared none

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How to cite this article

- Mandana Moradi, Sarah Mousavi. Drug use evaluation of diabetes mellitus in non-hospitalized patients. *Int J Pharm Pharm Sci* 2016;8(8):337-341.