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Therapeutic adherence: A prospective drug utilization study of oral hypoglycemic in patients with type 2 diabetes mellitus

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PEER REVIEW

ABSTRACT

Objective: To determine the drug utilization patterns and outcomes of treatment in terms of metabolic control in the type 2 diabetic patients on oral hypoglycemic agents in the outpatient department in the teaching hospital of Hamdard University, New Delhi, India.
Methods: Patients with established type 2 diabetes (*n*=184) visiting the outpatient department were interviewed using a structured questionnaire over a period of five months.
Results: Majority of the type 2 diabetic patients in this setting were treated with a multiple oral hypoglycemic agents. The most commonly prescribed oral hypoglycemic agent was biguanides (metformin) followed by sulfonylureas (glimepiride), thiazolidinediones (pioglitazone), alpha−glucosidase inhibitors (miglitol) and dipeptidyl peptidase−4 inhibitors (vildagliptin). As monotherapy metformin was the most common choice followed by glimepiride and voglibose, the most prevalent multiple therapy was a three−drug combination of glimepiride + metformin + pioglitazone. The study showed poor compliance to the prescribed therapy.
Conclusions: This study prospected the need of patient education and counselled to enhance the patient compliance for prescribed oral hypoglycemic agents and concomitant drugs. There is need for diet control as well as blood glucose and HbA1c monitoring. Metabolic control was found to be poor in the study population. HbA1c monitoring was underutilized. Clinical monitoring of patient's adherence to the prescribed treatment to achieve good glycemic control is recommended. Measures should be taken to improve patient´s adherence to the prescribed treatment.

1. Introduction

Diabetes mellitus is a metabolic disorder of multiple etiologies; characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both with characteristic symptoms of blurring of vision, thirst, polyuria and weight loss[1]. Several pathogenic processes are involved in the development of diabetes include the processes which destroy the beta cells of the pancreas with consequent

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insulin deficiency, and others that result in resistance to insulin action. The chronic hyperglycemia of diabetes is associated with long–term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. A continuous medical care is essential to prevent acute complications and to reduce the risk of long–term complications by patient's self–management and education[1]. The number of cases of diabetes worldwide in 2000 among adults ≥20 years of age is estimated to be 171 million and is projected to rise to 366 million in 2030. Based on sampling of studies from different parts of the world, the WHO has projected that the maximum increase in diabetes would occur in India[2]. In recent years, India has witnessed a rapidly exploding epidemic of diabetes[3,4]. Indeed, India today leads the world with largest number of diabetic subjects in any given country[4,5]. In 2000, WHO estimated that 31.7 million individuals were affected by diabetes in India and these numbers were expected to increase to 79.4 million by the year 2030[2]. Indians have a low risk threshold for diabetes because of many reasons[6].

Drug utilization review is a structured process used to assess the quality of drug therapy by engaging in the evaluation of data on drug prescribing, dispensing and/or patient use in a given health care environment against predetermined, agreed upon criteria and standards[7]. Drug utilization studies are powerful exploratory tools to ascertain the role of drugs in society. They create a sound socio–medical and health economic basis for health care decision–making[3]. When drug therapy is indicated, metabolic control depends on adherence to both non–pharmacological and pharmacological treatment. Tight blood glucose control has been correlated with a reduction in diabetic complications. Adherence to prescribed treatment is crucial to achieve this control. In the United Kingdom Prospective Diabetes Studies (UKPDS), patient's adherence to prescribed medications was 40–60%[8]. Drug utilization studies identify treatment adherence problems or reasons of non–adherence *i.e.*, whether inadequate control is due to missing doses or inadequate prescription. Thus, drug utilization studies design interventions to improve drug use. Drug utilization studies provide physicians with feedback on their performance[9]. They also assist to design educational programs that may improve prescribing and drug use.

The decision is made to carry out the study with the objective to determine the drug utilization patterns and outcomes of treatment in terms of metabolic control in the type 2 diabetic patients on oral hypoglycemic agents in the outpatient department of Majeedia Hospital, Jamia Hamdard, New Delhi, India.

2. Materials and methods

2.1. Study centre

The study was carried out in the outpatient department of Majeedia Hospital, Hamdard University, New Delhi, India. It was a prospective study of drug utilization patterns in diabetic patients.

2.2. Participants

The subject sample for this study consisted of 84 diabetic individuals. This study included type II (non–insulin–dependent) diabetes between the ages of 36 and 65 years. All subjects were recruited from clinics. All patients with established type 2 diabetes and those who were on oral hypoglycemic agents attending the hospital were included in the study during the time period of January 2010 to May 2010. Information on age, gender, weight, height, body mass index (BMI), waist to hip ratio (WHR), blood sugar levels, HbA1c levels, drugs prescribed and recommendations on diet and exercise were extracted from clinical records.

2.3. Procedure

Patients were interviewed after informed consent obtained. Interviews were conducted using structured questionnaire (open question method) by direct conversation. In the patient interviews, respondents were asked to either not follow the instructions at all or only follow them partly (noncompliance).

2.4. Measures

The morisky medication adherence scale was originally developed to assess compliance to medication in patients with hypertension and has also been used to measure adherence to antiretroviral therapy in patients who were HIV positive[10,11]. This simple 4–question survey assessed the likelihood that patients took their drug therapy as prescribed.

Morisky score was used to determine compliance by totaling the number of 'NO' answers to the 4 questions of non–adherence: whether they forget to take their medicine, are they careless to take medicine at times, when they feel better, whether they sometimes skip the dosing and when they feel worse, whether they take or stop the medication[12].

A higher score on the scale of 0–4 indicated better adherence to treatment (Yes=0; No=1). This technique is simple and straightforward and could be easily incorporated into patient care processes.

3. Results

3.1. Study sample characteristics

Total 184 patients with type 2 diabetes visited hospital out of which 81 (44.03%) were males and 103 (55.97%) were females. The mean age of the patients included in the study was (51.4±12.2) years. The mean BMI of the study population was (25.2±4.2) kg/m^2, as high as 71.2% male (40.02% female) of the study population (BMI>23 kg/m^2). The mean WHR of the female population was found to be 0.87±0.035 (higher than the acceptable limits of 0.85) and 0.89±0.031 in male population. About 58.7% (68.9% females) of the total diabetic patients had WHR more than the normal limits. Mean waist circumference of the female subjects was (83.46±8.5) cm (higher than the normal, 80 cm) and (85.13±7.39) cm in male subjects; close to 43.5% (59.2% females) of the total patients had waist circumference higher than the acceptable limits. A total of 27.2% patients had a positive family history of diabetes, 50.5% of the type 2 diabetic patients were having a history of diabetes since 2–5 years followed by 14.1% since 5–10 years where 79.9% of the total type 2 diabetic patients were non–

vegetarian.

3.2. Drug utilization patterns of oral hypoglycemic

Table 1
Utilization patterns of oral hypoglycemic agents.

Class	Drugs	No. of prescriptions	Percentage
Sulfonylureas	Glimepiride	109	26.3
	Gliclazide	9	2.2
	Glipizide	2	0.5
	Total	120	28.9
Biguanides	Metformin	143	34.5
Thiazolidinedione	Pioglitazone	79	19.1
	Rosiglitazone	5	1.2
	Total	84	20.3
a–Glucosidase inhibitors	Voglibose	8	1.93
	Miglitol	26	6.20
	Acarbose	8	1.93
	Total	42	10.14
DPP–4 inhibitors	Vildagliptin	19	4.59
	Sitagliptin	6	1.44
	Total	25	6.03
	Grand total	414	100

The average number of oral hypoglycemic agents per prescription was found to be 2.25. The data collected during this study showed that the most commonly prescribed oral hypoglycemic drug is metformin (34.5%), followed by the class sulfonylureas (28.9%), thiazolidinediones (20.3%), alpha–glucosidase inhibitors (10.14%) and DiPeptidyl Peptidase–4 (DPP4) (6.03%). Among sulfonylureas, glimepiride 109 (26.3%) was the most commonly prescribed drug followed by gliclazide 9 (2.2%) and glipizide 2 (0.5%) (Table 1). Among the thiazolidinediones, pioglitazone 79 (19.1%) was most commonly prescribed followed by rosiglitazone 5 (1.2%). Among the a–glucosidase inhibitors, miglitol 26 (6.2%) was the most commonly prescribed drug followed by voglibose and acarbose 8 (1.6%) respectively. Among DPP4 inhibitors vildagliptin 19 (4.59%) was most commonly prescribed drug followed by sitagliptin 6 (1.44%). Majority of the type 2 diabetic patients in this setting were treated with a multiple oral hypoglycemic therapy (71.7%) when compared to the single drug therapy (28.3%). Two–drug therapy was most prevalent (30.4%) followed by three–drug therapy (29.3%) and 4–drug therapy (12%). As monotherapy metformin was the most common choice followed by glimipiride (Table 2). Metformin was prescribed in 10.9% of the total type 2 diabetic patients. The most common two–drug therapy was a combination of glimepiride + metformin (13.04%) followed by vildagliptin + metformin (6.50%). The most prevalent three–drug therapy was glimepiride + metformin + pioglitazone (23.9%) and glimepiride + metformin +pioglitazone +miglitol (8.2%) was the most common four–drug combination prescribed (Table 3). In this study, 2.7% of patients showed an increase in dose within the study period. Dose reduction in the patient therapy was found to be 1.6% of the study subjects. In 14.1% of the patients, addition of another oral hypoglycemic therapy was initiated. It was found that 2.7% of patients switched to different agents within the study period. Concomitant disease in addition to diabetes was found in 67.9% of the patients. The most frequent concomitant chronic

condition of the study population was hypertension (46.7%) followed by dyslipidemia (13.1%).

Table 2
Oral hypoglycemic monotherapy.

Class	Drugs	No. of patients receiving monotherapy	% of patients receiving monotherapy
Sulfonylureas	Glimepiride	9	4.9
Biguanides	Metformin	20	10.9
Thiazolidinediones	Pioglitazone	2	1.1
a–Glucosidase inhibitors	Voglibose	8	4.3
	Miglitol	3	1.1
DPP4 inhibitors	Vildagliptin	7	3.8
	Sitagliptin	3	1.1

Table 3
Oral hypoglycemic agents multiple therapy.

Drug therapy	Combination therapy	No. of patients	%
2–drug therapy	Glimepiride + Metformin	24	13.04
	Gliclazide + Metformin	6	3.3
	Glimepiride + Pioglitazone	4	2.2
	Glipizide + Pioglitazone	2	1.1
	Metformin + Pioglitazone	3	1.6
	Metformin + Rosiglitazone	2	1.1
	Metformin + Vildagliptin	12	6.5
	Metformin + Sitagliptin	3	1.6
	Total	56	30.4
3–drug therapy	Glimepiride + Metformin + Pioglitazone	44	23.9
	Glimepiride + Metformin + Miglitol	4	2.2
	Gliclazide + metformin + Miglitol	1	0.5
	Glimepiride + Pioglitazone + Miglitol	2	1.1
	Gliclazide + Metformin + Pioglitazone	1	0.5
	Gliclazide + Pioglitazone + Acarbose	1	0.5
	Metformin + Rosiglitazone + Acarbose	1	0.5
	Total	54	29.3
4–drug therapy	Glimepiride+Metformin+Pioglitazone+Miglitol	15	8.2
	Glimepiride+Metformin+Pioglitazone+Acarbose	5	2.7
	Glimepiride+Metformin+Rosiglitazone+Acarbose	1	0.5
	Glimepiride+Metformin+Rosiglitazone+Miglitol	1	0.5
	Total	22	12

The data for fasting blood glucose (FBG) levels was available for 132 patients during the study period. The mean FBG of the type 2 diabetic patients was (161.8±75.7) mg%. Postprandial (PP) blood glucose levels data was available for only 90 patients during the study period. The mean PP blood glucose was found to be (239.0±109.1) mg%. The data for glycated hemoglobin was available for only 14 diabetic patients out of which 10 patients had HbA1c within the currently accepted range (*i.e.*, <7.0%). In the present study, only 48.4% patients have shown good adherence with the prescribed therapy (Table 4).

Table 4
Responses for the morisky medication adherence scale.

Morisky score	Male	Female	No. of patients	% of patients
0	3	2	5	2.7
1	12	24	36	19.6
2	20	34	54	29.3
3	36	35	71	38.6
4 (high adherence)	10	8	18	9.8

4. Discussion

The mean age of the patients (51 years) was less than that

reported in a study carried out in Spain (68 years)[13], and India (53 years)[14], and was more prevalent in the age group of 51–70 years indicating that type 2 diabetes is more prevalent in the middle–aged and elderly population.

Females predominated in the study population, which was similar to that reported in other studies in India[15] and Spain[13] but different from a study carried out in the United States[16], where the majority of the cohort was male.

In this study, the mean BMI of the study population was (25.4 ±4.5) kg/m^2, higher than the acceptable limits but less than that reported (30 kg/m^2) in Spanish study[13], and 71.20% (40.02% female) of the study population had a BMI >23 kg/m^2. A lower cut–off value of BMI (<23 kg/m^2) in Indian population when compared to western population was reported earlier in Indian studies[17,18]. The strong association between the BMI and diabetes indicated that even minor changes in BMI had adverse effects in this population.

In several ethnic populations including the relatively non–obese South Indian population, the android pattern of body fat, typified[19] by more upper body adiposity measured[20] as WHR was found to be a greater risk factor for type 2 diabetes than general obesity. Central obesity is common in Indians despite low rate of obesity[18]. Indians with low BMI have WHR comparable to the Mexican Americans, who are obese[21]. There had been an increase in the waist circumference and the WHR only increased in women over the years. WHR is strongly associated with insulin resistance and diabetes and this might explain the female predominance in the prevalence of diabetes in this population[19,22]. A total of 27.2% patients had a positive family history of diabetes. Majority of these are females and this goes with the fact that type 2 diabetes does not run in families.

The average number of antidiabetic drugs per prescription was found to be 2.25, which is higher than the previous records of 1.95[15] in India and less than 2.9[23], 2.27[7] that reported in Hong Kong and India respectively. The data collected during this study showed that the most commonly prescribed antidiabetic drug is metformin (34.5%), a biguanide, similar to that reported in earlier studies in Hong Kong[24] and England studies and different from that reported in previous Indian[7,15], Hong Kong[23], Bahrain[25] and Spain[13] where glibenclamide was reported to be the most commonly prescribed drug. The high metformin prescription rates reflect the post UKPDS phase in diabetes management where metformin was found to be superior to sulfonylureas[26]. Metformin is a peripheral sensitizer of insulin and has beneficial effects on insulin resistance, an important factor in pathogenesis of type 2 diabetes.

Metformin is the therapy of choice for overweight and obese patients with type 2 diabetes[27]. The effect of metformin is largely independent of body weight, age and duration of diabetes. It can be equally effective in normal weight patients. As monotherapy is in patients who are not adequately controlled on non–pharmacological therapy, optimally titrated metformin therapy typically reduces fasting plasma glucose by 2–4 mmol/L, corresponding to a decrease in HbA1c by approximately 1–2%[28]. Metformin is unlikely to cause severe hypoglycemia because it does not stimulate insulin release. Boccuzzi et al., reported the distribution of oral hypoglycemic agents as 66.4% sulfonylureas, 24.3% metformin, 6.6% troglitazone, 1.5% repaglinide, and 1.1% alpha–glucosidase inhibitors[16].

By the time, diabetes is diagnosed in type 2 diabetic patients,

pancreatic β–cells would have started failing. In lean and thin type 2 diabetic patients where pancreatic β–cell failure predominates, the choice of glimepiride is more justified. Glimepiride is more potent and yet behaves more like glipizide than glyburide, with good postprandial insulin response and a lower incidence of hypoglycemia than other sulfonylureas[29]. Decreased protein binding property of glimepride in patients with renal insufficiency results in unchanged elimination, makes it a safer option for patients with renal impairment[30]. Higher prescription rates of glimepiride also reflect the aggressive marketing of a new molecule in Indian market. The reason for lesser prescribing rates of other sulfonylureas is their adverse effect profile.

Among the thiazolidinediones, pioglitazone was most commonly prescribed followed by rosiglitazone. A lower prescribing rate of a–glucosidase inhibitors was noted in this study probably due to high cost and lack of studies showing long term benefits with these group of drugs. Among these, miglitol was the preferred choice because of its decreased gastrointestinal side effects.

Most patients with type 2 diabetes require a combination therapy to reach an acceptable level of glycemic control. Moreover, because type 2 diabetes mellitus is a progressive disease, even patients with a good initial response to oral agents eventually require a second (or third) medication[31]. As monotherapy, metformin was the most common choice followed by glimepiride. Metformin has been recommended as the first line treatment in obese patients with type 2 diabetes mellitus and the combined use of a sulfonylurea with metformin is often synergistic because of insulinogenic effect of the former[32] and the beneficial effects of the latter on insulin resistance[33]. Both of these factors are important in the pathogenesis of type 2 diabetes mellitus[1]. The high prescription rates of metformin alone and in combination with a sulfonylurea and/or thiazolidinedione correlate well with the relatively high BMI in our study population.

Increase in the doses for the oral hypoglycemic agents was not fairly common, with 2.7% of patients having an increase in dose within the study period. This was much less than that reported by Bocuzzi et al., 25.2%[16]. This reflects that the follow–up by the patients is poor. It was found that only 1.6% of the study subjects had a reduction in the initial dose of oral hypoglycemic agents within the study period which was also less than that reported previously, 10.92%[16]. The fewer changes observed in the dose and frequency of the treatment prescribed may be attributed to the short duration of the study.

Addition of another oral hypoglycemic therapy was initiated in 14.1% of the patients during the study period, less than that reported earlier, 14.7%[16]. It was found that 2.7% of patients switched to different agents within the study period, less than that reported previously, 10%[16]. The changes in the oral hypoglycemic agent treatment were not fairly common during the study period.

Concomitant disease in addition to diabetes, which was found to be proportionately less than that reported in a previous study, 87%[13]. Concomitant disease in form hypertention and dyslipidemia was found to be similar as reported in earlier studies[13,26]. Most commonly prescribed concomitant drugs in type 2 diabetic patients were in the order ACE inhibitors > multivitamins > statins > proton pump inhibitors > aspirin >

diuretics > b–blockers > antibiotics > NSAIDs > NSAIDs > CCBs. The use of multivitamins and proton pump inhibitors was found to be higher. Only 42.4% patients were having the FBG levels within the acceptable limits. The mean FBG of the type 2 diabetic patients was (162.8±76.7) mg%, higher than the acceptable limits (i.e., <130 mg%). This figure was however less than that reported earlier in Spain, 166 mg%[13] and higher than that reported in Indian studies, 156 mg%[14].

The mean PP blood glucose was found to be (240.0±110.1) mg% which is higher than that reported earlier in India, 226 mg%[14]. Only 33.9% of these patients had their PP blood glucose levels under control. The higher values of the blood sugar levels reflect the poor compliance of the patients with the therapy and with the prescribed blood sugar testing, poor physical activity and a poor awareness about the cut–off points.

The data for glycated hemoglobin was available for only 14 diabetic patients, out of which 10 patients had HbA1c within the currently accepted range, <7.0%[1]. Despite that HbA1c reflects the patient's metabolic control of preceding three months and patient adherence, the HbA1c monitoring in type 2 diabetic patients is underutilized in this hospital setting. This may be attributed to a high cost of this test, low awareness and lack of patient education. Patient adherence was calculated based on the scores of morisky medication adherence scale[34]. Morisky scale is a robust and useful tool for assessing patient's adherence to medication therapy. Morisky score is associated with HbA1c values; the better the adherence to the medical regimen, the lower the patient's HbA1c values. Only 48.3% of the study population showed good adherence with the prescribed therapy, which was found to be lesser than 85%[35], 67.2%[36] and higher than 44%[37] reported earlier. Good adherence (morisky score 3–4) was associated with a 10% lower total HbA1c value[34]. Metabolic control was found to be poor in this study population. More than half of the type 2 diabetic patients showed higher fasting and PP blood glucose levels than recommended. HbA1c monitoring was underutilized. Improved glycemic control is needed. More than half of the type 2 diabetic patients showed poor adherence to the prescribed therapy[7].

The result shows that measures should be taken to improve patient's adherence to prescribed medication which can be improved by comprehensive patient management which includes diet control, life–style modification, use of hypoglycemic, care and prevention of cardiovascular complications. It can be achieved by patient education and counseling for rational use of oral hypoglycemic and concomitant drugs, routine examinations (blood glucose and HbA1c levels), diet control as well as diabetic complications. Drug utilization studies should be carried out in a large population and at different locations in India so that the utilization patterns may be compared and improved further.

The present study was conducted on a small sample size for four–month duration only which is too short for comprehensive assessment of drug utilization in diabetic patients. The proposition of long term exhaustive studies on large sample size is being explored.

Conflict of interest statement

We declare that we have no potential conflict of interest.

Acknowledgements

Comments

Background

India is a vast country and diabetes is epedemic leading the world giving big burden over health care system. WHO estimated 31.7 million individuals were affected by diabetes in 2000 and expected to rise to 79.4 millions by the year 2030.

Research frontiers

Poor education and economy in Indians are major contraventions of patient compliance and negligence to prescribed medication. Use of interventions to improve adherence are rare in routine clinical practice in light of main theme of the article, so the authors have tackled one of the neglected aspect medical system.

Related reports

This study is at variance with the study done by Bocuzzi et al. with respect to the increase in the doses for the oral hypoglycemic agents, reduction in the initial dose of oral hypoglycemic agents, addition of another oral hypoglycemic agents and patients switched to different agents.

Innovations & breakthroughs

The present study identifies treatment adherence problems or reasons of non–adherence i.e., whether inadequate control is due to missing doses or inadequate prescription. Thus drug utilization studies design interventions to improve drug use.

Applications

It provides physicians with feedback on their performance. Drug utilization studies also assist to design educational programs that may improve prescribing and drug use minimizing prescription and medication error.

Peer review

This is a qualitative study carried out to analyze the drug utilization pattern in Indian medical system to diagnose the patient adherence to prescribed therapy. The authors

prospected the basic causes of non compliance, negligence of medication.

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