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Research Article

Glycemic control and cost-effectiveness attained by the drug utilization of oral antidiabetic agents in a tertiary care hospital in South India

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ABSTRACT

Background: Diabetes mellitus require lifelong intervention and Kerala has high prevalence. New expensive agents require comparison with existing regimens for cost-effectiveness.
Methods: Socio-demographic, anthropometric, FPG and HbA1C (baseline and post treatment) of 150 patients (73 men; 77 women) were obtained from records using standard case report forms in our retrospective study. ANOVA and paired t test were used for between groups and within group comparison.
Results: Metformin was maximum utilized (DDD/1000/day-252.39). All treatment regimens produced significant reduction in FPG (except metformin monotherapy) and HbA1C (except metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor combination). When compared to metformin sulfonylurea pioglitazone combination (best therapy), other regimens were less cost effective in reducing FPG and metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor was more effective and expensive in reducing HbA1C.
Conclusions: High prescription rates of metformin were due to its action on insulin resistance and weight. Addition of pioglitazone was cost effective and DPP-4 inhibitor was expensive but effective.

Keywords: ATC/DDD antidiabetic agent's cost-effectiveness analysis pioglitazone DPP-4 inhibitors

INTRODUCTION

Diabetes mellitus is a pandemic non communicable disease. India is often quoted as the 'diabetes capital of the world'.[1] though we do not have the largest population of diabetics or the highest prevalence of diabetes.[2] Reports of high prevalence of diabetes in south India dates back to the year 2000. The highest prevalence of diabetes reported so far from India has been from Ernakulum, where a prevalence of diabetes was 19.5%.[3] and a prevalence of type 2 diabetes mellitus (T2DM) of 16.3% has also been reported from Trivandrum.[4] Life long lifestyle modifications and medications are required for maintaining glycemic control in diabetics, which signifies the importance of knowledge about cost-effectiveness, hence this study. Pharmacoepidemiology is a discipline which is defined as the study of use of and the effect of drugs in large population.[5] Drug utilization studies are integral part of Pharmacoepidemiology. It describes the nature, determinants and extent of drug exposure and is powerful exploratory tools to ascertain the role of drugs in society.[6] They also assess the rationality of prescriptions, provide feedback and create awareness among prescribers. Prescription analysis can also be done according to WHO specified drug use indicators which can be used to assess the extent of drug use, which is expected to be appropriate, economical, safe, effective and according to treatment guidelines in a tertiary care teaching hospital.

The objectives of this study was to determine the drug utilization pattern, glycemic control and cost-

effectiveness of oral antidiabetic agents prescribed at diabetology outpatient of Sree Gokulam medical college and research foundation, Venjaramoodu, Trivandrum, India.

METHODS

Our study is a record based retrospective study of 150 T2DM patients diagnosed and treated by diabetologist for more than 6 months were analysed. Sample size was calculated by assuming α as 0.05 and β as 0.2 and a power of 80%. Patients who attended the diabetology outpatient between 1st December 2012 and 1st December 2013 were included in the study. Newly detected diabetics, patients on insulin and those who had a regimen change in the study period were excluded from the study. Institutional ethics committee clearance was obtained prior to commencing the study and written informed consent was waivered since no intervention was done, identifying details of patients were not collected and there was no direct patient interaction. Two values of fasting plasma glucose (FPG) and glycated haemoglobin (HbA1C), pre-treatment and one year post treatment were obtained from medical records of the patients enrolled along with co-morbidities, co-prescribed medications, antidiabetic agents used, socio-demographic, anthropometric data in standard case record form. Defined daily dose (DDD) for each drug was obtained from WHO ATC index, DDD/1000/day and prescribed daily dose (PDD) was calculated using the formula 1 and 2 respectively.[6,7]

1. $$\frac{\text{Total number of dosage units prescribed} \times \text{strength of each dosage unit} \times 1000}{\text{DDD} \times \text{Duration of study} \times \text{total sample size.}^{6}}$$

2. $$\frac{\text{Total number of dosage units prescribed} \times \text{strength of each dosage unit}}{\text{Number of patients who were prescribed the medication.}^{7}}$$

Cost, strength and composition of brands of medicines were obtained from www.cimsasia.com. Cost-effectiveness analysis was done for five most frequently prescribed treatment regimens. Average cost-effectiveness ratio (ACER) was calculated by dividing the cost of treatment regimen per day by difference produced by treatment in the health outcome. Incremental cost-effectiveness ratio (ICER) was calculated using the formula by considering one treatment regimen as the best treatment.[8]

$$\frac{[\text{Cost of drug A} - \text{Cost of drug B}]}{(\text{Difference in outcome measure produced by drug A} - \text{Difference in outcome measure produced by drug B})^{8}}$$

Where A is the assumed best treatment regimen and B other treatment regimens.

Statistical analysis was done using R software® using descriptive statistics. Values are expressed as mean±standard error of mean and rounded off to single decimal. Between group comparisons of baseline characteristics, reduction in FPG and HbA1C was done using ANOVA and paired t test was used for within group comparison of FPG and HbA1C. A p value <0.05 was considered statistically significant. Incremental cost-effectiveness plots were obtained from http://www.healthstrategy.com.

RESULTS

1044 prescriptions of patients in the age range of 28 to 83 were analysed. Average number of prescriptions were per patient per year was 6.96. The mean BMI, age and duration of diabetes were 24.6±0.2 kg/m^2, 55.1±0.8 years and 5.3±0.4 years respectively. There was no significant difference in baseline characteristics of the patients included in the study (Table 1).

Table1: Baseline characteristics of T2DM patients.

Gender	n (%)	BMI (kg/m^2)	Age (years)	Duration of diabetes (years)
Female	77 (51.3%)	24.9±0.3	54.5±1.1	4.9±0.5
Male	73 (48.7%)	24.4±0.3	55.6±1.3	5.6±0.6

Prescription pattern analysis showed the average number of antidiabetic agent prescribed per patient was 2.2±0.1. Combination therapy (n=111) was preferred over monotherapy (n=39) of which dual antidiabetic agents (n=55) were preferred. Three and four antidiabetic agents were prescribed for 43 and 13 patients respectively. Among the monotherapy agents metformin (n=34) was the prescribers favourite followed by sulfonylurea (n=4) and DPP-4 inhibitors (n=1). Antidiabetic agents prescribed in the decreasing order of frequency were metformin (n=143), sulfonylurea (n=99), α-glucosidase inhibitors (n=42), DPP-4 inhibitors (n=24) and pioglitazone (n=16). Among the sulfonylureas, the use of glimepiride (n=73) was favoured, glibenclamide (n=16), gliclazide (n=7), glipizide (n=3) were infrequent used. Among the 42 prescriptions for α-glucosidase inhibitors 41 were of voglibose 1 was acarbose and miglitol was not prescribed. Vildaglipitn (n=23) and sitaglipitin (n=1) were the prescribed DPP-4 inhibitors.

The most frequently used treatment regimen (Table 2) was metformin sulfonylurea combination (n=46), of which 33 patients were prescribed metformin glimepiride combination. Other frequent treatment regimens were metformin monotherapy (n=34) and combinations of metformin sulfonylurea α-glucosidase inhibitor (n=24), metformin sulfonyl urea pioglitazone (n=8) and metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor (n=8). Infrequent regimens (n=30) included

monotherapy with agents other than metformin and various other combinations of these agents. Drug utilization (Table 3) as per defined daily dose (DDD/1000/day) showed metformin (DDD/1000/day - 252.4) as the most utilized. Other highly utilized agents were glimepiride (215.3), vildaglipitn (40.1), gliclazide (32.5) and pioglitazone (31.6). Sitagliptin (3.1) and acarbose (0.5) were the least utilized. Prescribed daily dose were lower than DDD for all agents except gliclazide and acarbose which were prescribed at higher doses and sitagliptin similar dose as DDD.

Table 2: Treatment regimens of T2DM patients.

Treatment regimens	n (%)
MET+SU	46 (30.7%)
MET	34 (22.7%)
MET+SU+AGI	24 (16%)
MET+SU+PIO	8 (5.3%)
MET+SU+AGI+DPP-4 I	8 (5.3%)
Other regimens	30 (20%)

Met-metformin, SU-sulfonylurea, AGI-α glucosidase inhibitor, PIO-pioglitazone, DPP -4 I-dipeptidyl peptidase-4 inhibitor.

Five most frequently prescribed treatment regimens were analysed for baseline variability (Table 4). Metformin sulfonylurea α-glucosidase inhibitor combination and metformin sulfonylurea pioglitazone combination had significant longer duration of diabetes compared to metformin monotherapy. Pre-treatment HbA1C showed statistically significant lower value for metformin monotherapy. No other differences were observed between groups.

All groups except metformin monotherapy showed significant reduction in FPG and all groups except metformin sulfonylurea pioglitazone combination showed significant reduction in HbA1C when compared using 'paired t test' (Table 5 and Figure 1, 2). Between groups, comparison of reduction of HbA1C showed no significant difference hence reduction in FPG and proportion of patients attaining ADA glycemic goal (HbA1C<7) was used to determine the best treatment regimen for incremental cost effectiveness ratio (ICER). Metformin sulfonylurea pioglitazone combination produced significant reduction in FPG compared to 3 other groups and had the maximum proportion of patients attaining ADA goal for diabetics (50%). Least proportion of patients attaining ADA goal was under metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor combination regimen.

Table3: DDD/1000/day and prescribed daily dose (PDD) of various antidiabetic agents.

Antidiabetic agent	ATC code	Defined daily dose (DDD)	DDD/1000 /day	Prescribed daily dose (PDD)
Metformin	A10BA02	2 g	252.4	1.1±0.1 gm/ user/ day
Glimepiride	A10BB12	2 mg	215.3	1.9±0.1 mg/user/day
Vildagliptin	A10BH02	0.1g	40.1	56.5±4.2 mg/user/day
Gliclazide	A10BB09	60 mg	32.5	90.3±13.3 mg/user/day
Pioglitazone	A10BG03	30 mg	31.6	19.2±2.4 mg/user/day
Glibenclamide	A10BB01	7 mg	15.9	2.2±0.1 mg/user/day
Glipizide	A10BB07	10 mg	7.7	8.3±1.7 mg/user/day
Sitagliptin	A10BH01	0.1 g	3.1	100 mg/user/day
Acarbose	A10BF01	0.3 g	0.5	50 mg/user/day
Voglibose	A10BF03	-*		0.4±0.03 mg/user/day

* DDD not defined by ATC index

Table 4: Baseline characteristics of patients in frequently prescribed treatment regimens.

Regimen (n)	Age (years)	BMI (kg/m2)	Duration of diabetes (years)	Pre-treatment FPG	Pre-treatment HbA1C
MET (n=34)	50.4 ±1.8	24.5±0.4	3.0±0.5	145.1±6.1	7.3±0.2**
MET+SU (n=46)	56.6 ±1.5	24.7±0.4	4.96±0.7	147.2±6.4	7.6±0.2
MET+SU+AGI (n=24)	58.2±1.8	23.9±.5	7.1±1.3*	145.5±8.2	7.8±0.3
MET+SU+PIO (n=8)	54.8±2.4	25.8±1.2	8.4±1.2*	188.3±21.5	7.5±0.5
MET+SU+AGI+ DPP-4 I (n=8)	56.4±3.1	24.9±1.3	5.3±1.2	140.6±13.4	7.8±0.2

MET- metformin; SU- sulfonylurea, AGI- α-glucosidase inhibitor; PIO- pioglitazone; DPP -4I- dipeptidyl peptidase - 4 inhibitor
*indicates statistically significant higher value using ANOVA compared to metformin group; ** indicates statistically significant lower value using ANOVA compared to other groups.

Mean cost of medications per patient per year was 9293.1±483.6 INR, of which cost of antidiabetic agents were 5053.7±371.8 INR and cost of co-prescribed medications were 4310.3±338.5 INR. Metformin monotherapy was the most economic treatment. Average cost-effectiveness ratio for unit reduction in FPG and HbA1C per day was 20 paisa and 6 INR respectively for metformin monotherapy and, 11 paisa and 39 INR respectively for metformin sulfonylurea combination. Most effective treatment regimen according to our study, metformin sulfonylurea pioglitazone combination showed an average cost of 1 and 121 INR for unit reduction of FPG and HbA1C. Newest member, DPP-4 inhibitors proved to be effective in controlling blood glucose when combined with other medications but was found to be expensive (7.2 and 752.88 INR for unit reduction of FPG and HbA1C). Incremental cost-effectiveness ratio (ICER) (Table 6 and Figure 3, 4) in reducing FPG, considering metformin sulfonylurea pioglitazone as best treatment regimen, showed that metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor combination as less effective and more expensive. All the other treatment regimens are less effective and less expensive. ICER for reduction in HbA1C (considering metformin sulfonylurea pioglitazone as best treatment) showed all treatment regimens were less costly and less expensive except metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor combination which is more effective and more expensive.

Table 5: Comparison of FPG and HbA1C pre-treatment and 1 year post treatment.

Regimen (n)	FPG (mg/dl)			HbA1C (%)			Proportion of patients attaining HbA1C <7
	Pre-treatment	Post-treatment	Reduction	Pre-treatment	Post-treatment	Reduction	
MET[34]	145.1±6.3	135.8±4 (p=0.081)	22.98±3.8	7.3±0.2 ***	6.8±0.1* (p <0.01)	0.6±0.1	14 (41.2%)
MET+SU[46]	147.2±6.4	129±3.8* (p <0.05)	20.2±6.6	7.6±0.2	7.1±0.1* (p <0.01)	0.6±0.1	19 (41.3%)
MET+SU+AGI[24]	145.5±8.2	124.1±3.7* (p <0.01)	21.4±6.9	7.8±0.3	7.2±0.2* (p <0.01)	0.6±0.2	11 (45.8%)
MET+SU+ PIO[8]	188.3±21.5	117.3±5.9* (p <0.05)	71± 23.6**	7.5±0.5	6.8±0.2 (p =0.1)	0.7±0.4	4 (50%)
MET+SU+AGI +DPP-4 I[8]	140.6±13.4	108.3±13.6* (p<0.01)	32.4±8.7	7.8±0.2	6.9±0.1* (p <0.01)	0.9±0.2	2 (25%)

Met-metformin; SU- sulfonylurea; AGI- α-glucosidase inhibitor; PIO- pioglitazone; DPP -4 I- dipeptidyl peptidase - 4 inhibitor; *indicates significant reduction in post treatment value by paired t test ($p < 0.05$); ** indicates significant reduction in FPG when compared to other groups by ANOVA ($p < 0.05$); *** indicates significant lower pre-treatment value compared to other groups by ANOVA ($p < 0.05$).

Table 6: Cost-effectiveness of various treatment regimens.

Regimen (n)	ICER for FPG reduction (INR/mg/dl/day)	ICER for HbA1C reduction (INR/%/day)	ACER for FPG reduction (INR/mg/dl/day)	ACER for HbA1C reduction (INR/mg/dl/day)
MET (n=34)	0.7	183.8	0.2±0.2	6.0±2.6
MET+SU (n=46)	0.4	116.5	0.1±1.1	38.5±11.9
MET+SU+AGI (n=24)	0.2	144.5	0.9±1.1	81.2±26.3
MET+SU+PIO (n=8)	-	-	1.3±0.4	120.8±53.3
MET+SU+AGI +DPP-4 I (n=8)	-5.3*	927.9	7.2±5.95	752.9±317.2
MET (n=34)	0.7	183.8	0.2±0.2	6.0±2.6

Met-metformin; SU- sulfonylurea; AGI- α-glucosidase inhibitor; PIO- pioglitazone; DPP -4 I- dipeptidyl peptidase - 4 inhibitor; *Negative value indicates either the drug is more expensive or more effective than best treatment.

Among the co-morbidities (n=249), dyslipidemia (n= 87) was most common followed by systemic hypertension (n=73), coronary artery disease (n=43) and hypothyroidism (n=15). Co-prescribed medications included hypolipidemic agents (n=90), antiplatelet agents (n=62), angiotensin receptor blockers (n=49), multivitamin (n=44), beta blockers (n=24), thyroxine (n=17) calcium channel blockers (n=13), diuretics (n=10), ACE inhibitors (n=7), proton pump inhibitors (n=7), respiratory medications (n=5), iron and calcium (n=3) and other medications (n=13).

Atorvastatin (n=69), low dose aspirin (n=55) were the frequently co-prescribed medications.

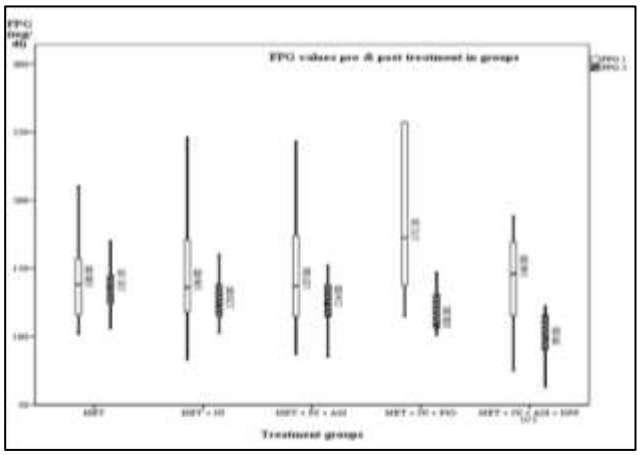

Figure 1: Box and whisker plot showing pre-treatment and post-treatment FPG in treatment groups.

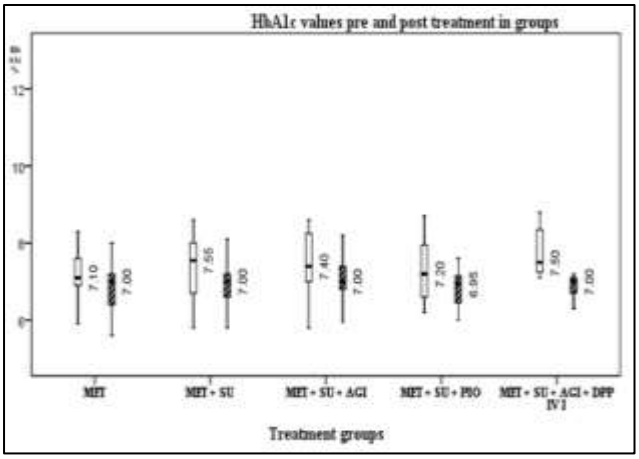

Figure 2: Box and whisker plot showing pre-treatment and post-treatment HbA1C in treatment groups.

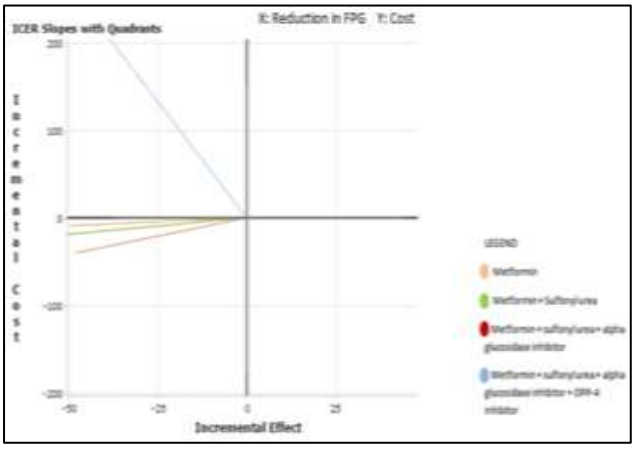

Figure 3: ICER plot for different treatment regimens in reducing FPG.

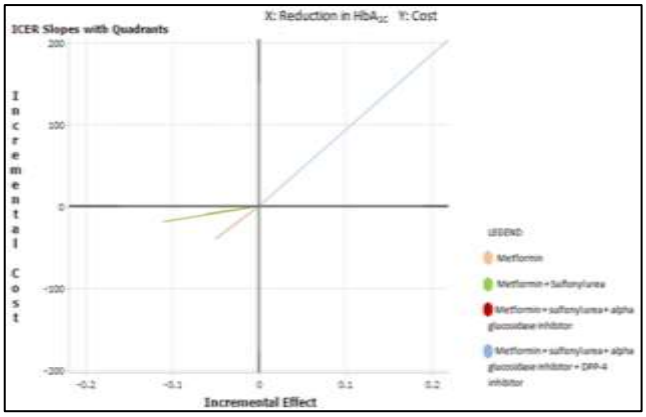

Figure 4: ICER plot for different treatment regimens in reducing FPG.

WHO drug use indicators were

- Encounter with an antibiotic prescribed - 5.3%
- Encounter with an injection prescribed - 8%
- Percentage of drugs prescribed by generic name - 5.3%
- Percentage of patients treated without drugs-Nil

Average drug cost per encounter ~ 9 INR

DISCUSSION

In our study, mean age and duration of diabetes was lower than previous reports from Kerala.[9] Probably due to increasing literacy rate and awareness among Keralites motivating them to seek early medical attention. The prevalence of diabetes was slightly higher in females in contrast to the national average.[10] The BMI of both males and females were in the overweight range for Asians.[11] and was higher than a previous study.[12] There was high prevalence of comorbidities, dyslipidemia (n=87), systemic hypertension (n=73), coronary artery disease (n=43) and hypothyroidism (n=15) similar to previous surveys.[9] The Asian Indian Phenotype.[13] Have an innate increased risk of these co-morbidities. These co-morbidities are also attributable to changing lifestyle habits such as sedentarism, fast food culture, which can be modified. 10% (n=15) prevalence of hypothyroidism was observed similar to previous reports.[14]

Prescription analysis showed a higher rate of prescription of metformin (n=143) due to its effective glycemic control without hypoglycaemia, low cost, weight loss, reduction of insulin resistance and compliance of treating physicians to treatment guidelines. Among sulfonylureas there is an increase in rate of prescription of glimepiride (n=73) since recent evidence suggest its favourable pleiotropic effects, cardiovascular beneficial effects and low incidence of hypoglycemia.[15] Glimepiride has been advocated as the sulfonylurea of choice in obese diabetics and south Asians.[16] Reduction in rate of prescription of glibenclamide (n=16) can be due to its higher incidence of hypoglycaemia and cardiovascular mortality on long term use.[15,17] Voglibose, which was approved a decade ago,

was prescribed for 41 patients and vildagliptin the newest and expensive agent was prescribed for 23 patients. α-glucosidase inhibitors provide adequate post prandial glycemic control among oral antidiabetic agents. Of which voglibose is the well tolerated and an efficacious agent which could be the reason for its high rates of prescription. Acarbose (n=1) and miglitol use was minimal owing to its gastrointestinal adverse effects such as flatulence, diarrhea and abdominal discomfort. DPP-4 inhibitors (n=24) have been advocated as second line agents due to its improved glycemic control over time, pleiotropic cardiovascular effects and pancreatic beta cell protective effects in animal studies.[18,19] Pioglitazone (n=16) prescription has declined in our study compared to the recent trend.[20] and was not used as monotherapy agent. This could be the repercussion of the ban and subsequent revoking of the ban and recent black box warning of pioglitazone as an agent causing increased risk of bladder carcinoma.[21] Combination therapy in T2DM is justifiable and often required for better glycemic control and for reducing adverse effects of individual agents. In our study, combination therapy was advocated for 111 patients, most common being metformin sulfonylurea combination (n=46). The rationale being, metformin reduces hepatic gluconeogenesis and decreases insulin resistance while sulfonylurea increases insulin secretions, which counter the two major pathologies in T2DM.[22]

Drug utilization showed an increase in utilization of metformin, glimepiride and a reduction in utilization of glibenclamide in contrast to earlier reports where glibenclamide was most utilized.[6] This is due to adherence to changing treatment guidelines, metformin's ability to reduce insulin resistance and weight without causing hypoglycemia.[23,24] On the other hand there is increased risk of hypoglycaemia, cardiovascular mortality and beta cell fatigue with long term use of glibenclamide.[19,25] Glimepiride on the other hand has favourable pleiotropic cardiovascular effects, low incidence of hypoglycaemia and is the preferred sulfonylurea in obese patients.[26-28]

Analysing FPG and HbA1C values, pre-treatment and 1 year post treatment of 5 commonly prescribed treatment groups showed that all treatment regimens showed significant reduction in FPG except metformin monotherapy. Fasting plasma glucose is a highly unreliable value for assessing glycemic control since it is dependent on previous day's diet, medication and exercise. All treatment groups except metformin sulfonylurea pioglitazone combination showed significant reduction of HbA1C. This may be explained on the basis of significantly longer duration of diabetes in this group, since efficacy of oral antidiabetic agents decrease as diabetes progresses.[19,25] The average cost of oral antidiabetic agents per year was ~5000 INR. Cost-effectiveness analysis showed metformin as the most economical therapy, which produced significant reduction in HbA1C. Since there was no significant difference in reduction of HbA1C between groups, reduction in FPG was considered the parameter for selecting most effective therapy which was metformin sulfonylurea pioglitazone combination. Incremental cost-effectiveness ratio when calculated with the most economic treatment showed an additional expenditure of ~ 60 paisa per day for 1mg/dl reduction of FPG and ~183 INR per day for 1% reduction of HbA1C. When analysed with the most frequently prescribed treatment regimen (metformin sulfonylurea combination), extra expenditure of 35 paisa per day for 1mg/dl reduction of FPG and 113 INR per day for 1% reduction of HbA1C was seen. ICER showed metformin sulfonylurea α-glucosidase inhibitor DPP-4 inhibitor combination as more effective and more expensive in reducing HbA1C.

Out of the total expenditure of ~9000 INR per year INR 4300 was for co-prescribed medications. This increased expenditure in health care industry is partly due to prescription of expensive treatments and partly due to modifiable risk factors which causes morbidity. Mean cost per prescription was ~ 9 INR. Among co-prescribed medications hypolipidemic agents (n=90) were most prescribed owing to the higher incidence of dyslipidemia. Antiplatelet agents (n=62), drugs acting on RAAS (n=56), multivitamin (n=44), beta blockers (n=24), thyroxine (n=17), calcium channel blockers (n=13) and diuretics (n=10) were also used. These are corresponding to the comorbidities, highest being dyslipidemia and hypertension which were similar to previous studies.9. 76% of patients with dyslipidemia were prescribed atorvastatin and 21.1% rosuvastatin, though rosuvastatin is more potent, economical and alteration produced in HbA1C is less compared to atorvastatin.[29,30] Angiotensin receptor blockers (n=49), beta blockers (n=24), calcium channel blockers (n=13), diuretics (n=10) and ACE inhibitors (n=7) were the antihypertensive used. The high frequency of prescription of drugs acting on RAAS might be due to cardioprotective and renoprotective effects of these drugs in diabetic hypertensive. Thiazide diuretics in optimal doses were prescribed to eight patients as add on therapy. These agents are preferred in low doses for diabetic hypertensives.[31] due to its lower propensity to producing metabolic effects. Cardio selective beta blockers were prescribed for control of hypertension in 24 patients. This cannot be considered judicious although there is increased avocations of its use in diabetics.[32] as they are contraindicated in patients with hypoglycemic episodes and hypoglycemic unawareness and theoretically they produce hyperglycemia, alter insulin sensitivity and lipid profile.[33,34] Most commonly used antiplatelet agent was low dose aspirin which is consistent with current trend. The drug combinations used for treatment of diabetes and co-morbidities were appropriate. Encounters with antibiotic prescribed was 5.3% which was higher than a previous study and with injections prescribed was 8.7% which showed lower value than previous study.[6] Only 5.3% prescriptions were generic which implies the need for generic prescriptions.

A limitation of this study was small sample size and baseline variability is the limitations of our study. A further study with analysis of post prandial blood glucose is required since it is a better predictor of cardiovascular complications of diabetes.

CONCLUSION

High prescription rates of metformin were due to its action on insulin resistance and weight. Addition of pioglitazone was cost effective and DPP-4 inhibitor was expensive but effective.

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