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PHARMACOECONOMIC EVALUATION OF EMPAGLIFLOZIN AS AN ADD-ON THERAPY IN TYPE-2 DIABETES HYPERTENSIVE PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Newer anti-diabetic drugs are predicted to have cardio-renal safety and fewer adverse effects than conventional anti-diabetic drugs, but their high cost is a key barrier to their usage. A prospective observational study involving 200 type 2 diabetes mellitus (T2DM) patients with hypertension who visited Endocrine out-patient clinics of SKIMS, a tertiary care referral hospital. Empagliflozin 25 mg (SGLT-2 inhibitor) was administered as an add-on therapy with metformin, teneligliptin and glimepiride for three months. Efficacy, quality of life and treatment cost in addition to direct and indirect cost parameters were assessed before addition

of empagliflozin and three months following empagliflozin treatment. In addition, the incremental cost-effectiveness ration (ICER) was computed. The mean age of the patients was 49.83±9.36 years. During the research period, empagliflozin showed significant ($p<0.05$) improvement in efficacy (total quality of life). Conventional anti-diabetics had lower direct medical costs and total treatment costs than empagliflozin. According to ICER, empagliflozin requires an extra USD 68.05 due to a reduction in effectiveness parameters. As an add-on therapy, empagliflozin has shown higher efficacy than conventional anti-diabetics.

KEYWORDS: Empagliflozin; Type 2 diabetes; Hypertension; Direct cost; Indirect cost; Pharmacotherapy.

INTRODUCTION

As the burden of diabetes and its serious long term complications is rising globally, it is being projected as a silent pandemic. India is the second most diabetes-affected country in the world. In 2019, diabetes was estimated to affect 77 million people in India and this figure is projected to be more than 134 million by 2045 [1]. Type 2 diabetes (T2D) and hypertension possess a bidirectional relationship and generally co-exist. The coexistence of T2D with hypertension affects the treatment outcomes, enhances the risk of cardiovascular diseases, alters quality of life and may lead to death. Therefore, it is imperative to develop treatment regimens which possess the potential to improve the clinical outcomes as well as quality of lives (QoL) [2]. Diabetes generally influences various aspects of QoL, though there may be changes based on ethnicity, environment, gender, socioeconomic level, culture, occupation or dietary habits. When complications develop or comorbidities manifest, a diabetic patient's QoL worsens further [3].

Empagliflozin is a sodium glucose co-transporter-2 (SGLT2) inhibitor which improves hyperglycemia in T2DM patients by decreasing renal glucose reabsorption. It regulates blood sugar levels without requiring insulin [4]. It has been found effective in T2DM diabetes inadequately controlled with metformin, glimepiride and dipeptidyl peptide 4 inhibitors [5].

Diabetes is also linked to increased pharmacy-related costs. Although SGLT-2 inhibitors are indicated as a suitable adjunct treatment to metformin, they are prohibitively costly [6, 7]. Clinicians have numerous safe and effective diabetic therapy choices that can lower HbA1c. SGLT-2 inhibitors are the most recently developed family of treatments, with a unique mechanism of action, excellent glycemic effectiveness, and cardiovascular and renal advantages observed in the EMPA-REG trials [8]. Odegard and gray conducted survey on poorly controlled diabetes and reported that cost of antidiabetic drugs was a major concern of medication noncompliance [9]. An economic study of Type 2 diabetes mellitus treatments is crucial to ensuring that limited resources are spent properly.

Because there is so much variety across different antidiabetics in terms of efficacy, quality of life, and cost profiles, it is extremely difficult for a physician or endocrinologist to deliver quality patient care at the lowest possible cost in antidiabetics. Due to the scarcity of studies comparing the cost-effectiveness of various newer antidiabetics as an add-on therapy to conventional antidiabetics, it is difficult to determine whether the incremental cost of newer antidiabetics is worth paying in terms of greater efficacy and safety as an add-on therapy when the target for efficacy is not met. The current study's ICER data may aid in decision-making in the Indian healthcare system on an individualised or

case-by-case basis, based on socioeconomic status with comorbidity.

This study assessed the effectiveness, quality of life, and cost of treatment of antidiabetic medicine, empagliflozin, as an add-on therapy to conventional antidiabetics during a three-month period in type 2 diabetes patients with hypertension.

MATERIALS AND METHODS

Design of The Study

This prospective, observational research study was conducted from October 2020 to October 2021 at the Departments of Endocrinology and Clinical Pharmacology; Sher I Kashmir deemed university in a tertiary care hospital. The research was approved by Committee on Institutional Ethics with Protocol number [RP 29/2020 (IEC-SKIMS/2020-591)] in accordance with ethical guidelines of ICH-GCP by Indian Council of Medical Research (ICMR). Standards of good clinical practice (GCP) and revised version of the declaration of Helsinki were followed in this study. Prior to the trial, the study participants acquired written informed consents. Confidentiality and secrecy of their identity were ensured of each and every participant.

Selecting a Patient

Age above 18 years with T2D and hypertension; uncontrolled hypertension (systolic blood pressure [SBP] ≥ 130 mmHg and diastolic blood pressure [DBP] ≥ 80 mmHg or more); HbA1c ≥ 6.5 %; patient on triple drug therapy- metformin (upto 2 g/day), teneligliptin (20 mg/day) and glimepiride (upto 8 mg/day) for not less than last 3 months. Exclusion criteria: Chronic liver disease, chronic kidney disease - stage 4 and 5, pregnancy/lactation, refusal to consent, history of severe allergy to any drug and those who accepted insulin therapy for uncontrolled blood glucose. Also, endocrinologist judgment was considered final for inclusion and exclusion of patient.

RESEARCH METHODOLOGY

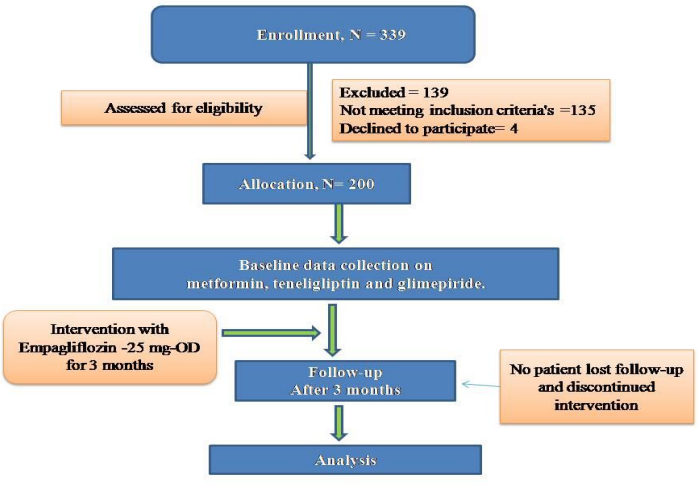

Figure 1. Methodology Profile

When patients satisfied the inclusion criteria, their check-up visit was considered the baseline of the trial, and blood samples were checked for efficacy parameters as

baseline data. The individuals were given the allocated therapy, and a three-month follow-up was performed. The individuals were examined for changes in HbA1c, fasting plasma glucose, post-prandial plasma glucose, systolic blood pressure, and diastolic blood pressure at the conclusion of three months of therapy. As a result, data on comprehensive demographics, diabetes history, and antidiabetic medication information, treatment effectiveness metrics, and treatment cost were obtained using a case report form. Enrolled patients were followed up on for three months, and the following information was also obtained at the conclusion of the three months. In the interim, patients were contacted by phone for further study-related information.

Evaluation of Treatment Efficacy

Changes in HbA1c, fasting plasma glucose, post-prandial plasma glucose, systolic and diastolic blood pressure, and quality of life were used to assess the efficacy of newer antidiabetics treatments. The status of effectiveness parameters was determined by comparing the parameters in the three months preceding the study's beginning to the efficacy parameters data collected during the three months of the study. A manually generated case report form was used to collect socio-demographic information such as age, gender, education level, and marital status in addition to clinical data such as diabetes duration. The quality of life instrument in diabetes was used to evaluate the total quality of life at baseline and follow-up for participants in this study for patients of north Indian diabetes patients, and it consists of 34 items covering eight domains (including role limitations due to physical health, physical endurance, general health, treatment satisfaction, symptom botherness, financial worries, mental health, and diet satisfaction) [10].

Treatment Cost

Patients' treatment expenditures were separated into direct and indirect charges. Direct costs covered both direct medical and direct non-medical expenses. Direct and indirect expenses are easily quantifiable in monetary terms. The patients were given a well-designed case report form on which to record the cost-related factors. Because the cost of each parameter (medication, examinations, food, and so on) might vary depending on location, time, and a person's financial situation, a case report form was employed in this study to ensure uniformity in the cost computation for all individuals. (The cost was computed using 1 USD and 75.385 INR as of October 13, 2021) [11].

Direct Medical Expenses

Direct medical expenditures were associated with medical treatments and included the cost of anti-diabetic medications and laboratory tests throughout the three-month follow-up period. The cost of the drugs was determined using the Current Index of Medical Specialties (Current Index of Medical Specialties, 2020–21) [12] and the total number of doses of medicine used during a three-month period. This was also done for drugs that were covered by the insurance/reimbursement plan. The difference in antidiabetic dosage over the research period was also taken into account when calculating the total cost of medicine. The results of investigations performed at our institution during the research period were computed using the Revised Rates of SKIMS Investigation Charges, SIMS 138/68/2019, dated March 15, 2019 [13]. Cost of medicine for 3 months = day × 30 days × 3 months.

Non-Medical Direct Costs

Transportation charges are an example of direct non-medical costs (excluding expenses for attendants). The patient's journey to our hospital in Srinagar was calculated using northern trains (Fares Tables, 2020-2021). Patients were asked how many days they stayed for treatment (including stays at relatives' homes) during the study period, and lodging costs were calculated based on the daily allowance given for the lowest pay level in the pay matrix of the Seventh Pay Commission's Travelling Allowance Rules, which was USD 5.96 (INR 450) per day (Travelling allowance rules, 2018). The food expenditures incurred throughout their journey and stay duration were calculated; if they were less than USD 6.68 (INR 500) per day, they were taken into account as actual. If patients expressed it as more than USD 6.63 (INR 500) per day, then USD 6.63 (INR 500) per day was considered as the minimum reimbursement given for food for the lowest pay level in the pay matrix of the Travelling Allowance Rules of the Seventh Pay Commission, by the Ministry of Finance, Government of India, Travelling allowance rules, 2018.

Indirect Expenditures

An indirect cost is the expense borne by patients (excluding the attendant's loss) owing to loss of productivity or absenteeism from work due to an appointment. The patients were notified of the salary loss as a result of the hospital visit. The cost was estimated by taking into consideration the minimum wage set by the Labour Department, Office of Labour Commission (Skill Labour Department Notification, 2017) [14].

- Un-skilled- (INR 225 USD 2.98 per day.
- Skilled- (INR 350 USD 4.64 per day.
- Highly skilled- (INR 400 USD 5.30 per day.
- Administrative/ ministerial/ account staff- (INR 325 USD 4.31 per day.

DATA ANALYSIS

For parametric data, data was reported as mean SD or percentage, while for non-parametric data, data was expressed as median. For parametric data comparison, the Student's t-test was employed, and for non-parametric data comparison, the Mann-Whitney U test was employed. P-values of less than 0.05 were considered statistically significant. The incremental cost-effectiveness ratio (ICER) was determined by dividing the change in total expenses (incremental cost) by the difference in health care outcome measure or effect (incremental effect). It gave a cost-benefit ratio for each unit of health outcome change, assisting in the selection of cost-effective therapy. The following formula was used to calculate the ICER.

$$ICER = \frac{CostA — CostB}{EffectA — EffectB}$$

RESULTS

A total of 200 type 2 diabetes patients with hypertension were recruited, with a mean age of (49.83 ± 9.36) years, 37.5 percent of men and 62.5 percent of females, and 96.5 percent married. The majority of respondents (40%) were graduates or undergraduates, with 14.5 percent being illiterate. The majority of the patients (96.5%) were married; 60.5 percent were from rural areas; and 64 percent and 36%, respectively, were from low- and moderate-income families. At the end of the treatment, patients showed significant decreases in systolic blood pressure, diastolic blood pressure, fast blood pressure, post prandial glucose and glycemic haemoglobin (follow-up). In comparison with baseline data, the study revealed $P<0.05$ significant decrease of SBP, DBP, FBG, PPG and HbA1C.

According to the QoL analysis, total quality of life has increased when compared to the baseline quality of life in Table 2. Between baseline and follow-up QoL data scores, there were significant differences (*P<0.05) in the role of limitations due to physical health, physical endurance, general health, symptom botherness, financial worries, emotional/mental diet, and diet satisfaction. Overall, followup scores were found to be significantly (*P<0.05) higher (empagliflozin as an add-on therapy).

TABLE 1. Change In Qol Scores In Baseline And Follow-Up During Treatment

Domains	**Items**	**Baseline (Mean score)**	**Follow-up (Mean score)**	**P value**	**Minimum**	**Maximum**
QOLID score	34	84.81 ± 9.593	120.7 ± 6.815	< 0.0001	34	169

Data were presented as mean and SD. calculated by Wilcoxon matched-pairs signed rank test and used to assess the change in QOL score at follow-up.*P<0.05 was considered as significant. The assessment of health related quality of life was done by QOLID scale. The patients were asked to evaluate their perception. The patients perception were evaluated on baseline and followup (after 3 months of empagliflozin as an add on therapy).

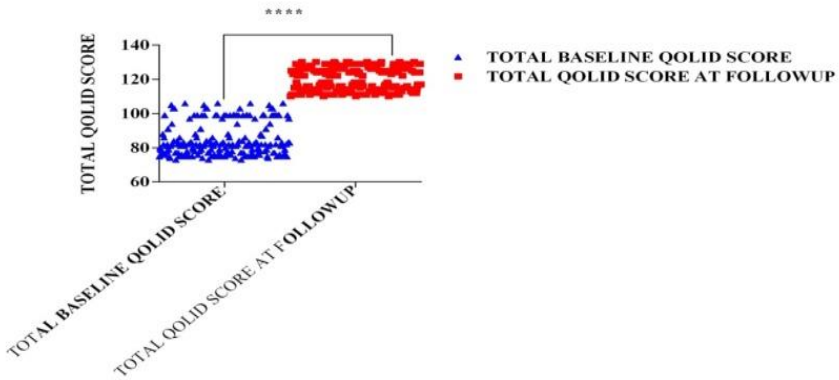

Figure 2. Change In Total Qolid Scores In Baseline And Follow-Up During Treatment

In this figure each triangle and circle corresponds to one patient (n=200) in baseline and followup respectively, the sample t test was used to compute the mean values. The range of score in role of limitation in physical health and physical endurance domain was 6-30. In general health domain the range was 3-15, whereas, in treatment satisfaction domain the range was 4-20. In symptom botherness, financial worries, emotional/mental health and diet satisfaction domain the range was 3-15, 4-19, 5-25 and 3-15 respectively. In total QoL score the range is in between [34 – 169], P value <0.05 was considered as significant. ****p<0.0001

The direct medical cost in the newer antidiabetic group (empagliflozin) as an add-on therapy with standard antidiabetics [Metformin (2g/day), Teneligliptin (20 mg/day), and Glimepiride (8 mg/day)] was high [USD 68.05 (IQR 106.61-38.56)]. Among the various components, expenditures for AEs management were not reported. Despite the fact that these components were included in the

computation of direct medical costs, the direct medical costs were exclusively determined by the cost of drugs.

TABLE 2. Illustrates a cost comparison between empagliflozin, a newer anti-diabetic therapy, and conventional antidiabetics.

Cost Parameters in USD mean	**At Enrollment with conventional drugs for last 3 months.**	**After 3 months of add on therapy with new antidiabetics (empagliflozin 25 mg-OD) Followup.**	**#Difference in cost**
Direct Medical Cost Cost of Medicines Cost of Cost of Investigations	38.56 2.52	106.61 2.52	68.05
Indirect Medical Cost including Transportation and Cost of Food	6.63	6.63	
Indirect Cost	5.3	5.3	
Total cost of treatment (direct medical + direct non-medical + indirect)	53.01	121.06	68.05

#additional cost for empagliflozin to improve the parameter by one unit as compared to standard diabetes therapy

Incremental Cost-Effectiveness (ICER)

According to the ICER study, the additional cost for more improvement in QOLID score for empagliflozin as a new antidiabetic therapy compared to conventional antidiabetics were USD 2.29 for 3 months of treatment. According to ICER, the cost of empagliflozin as a novel antidiabetic drug when used as add-on therapy to conventional antidiabetics were USD 109.40, 1.60, 0.93, 10.51, and 43.62 for decrease in effectiveness measures, namely HbA1C, FBG, PPG, SBP, and DBP after 3months of treatment (Table 3).

TABLE 3. Illustrates many cost characteristics and their comparisons between conventional and empagliflozin as a new antidiabetic drug.

Parameters	**At Enrollment with conventional drugs for last 3 months.**	**After 3 months of add on therapy with new antidiabetic (empagliflozin**	**Difference**	**Incremental cost-effectiveness (ICER)**

		25 mg-OD) Followup.		
The total treatment cost in USD	53.01	121.06	68.05	
Improvement in QOLID mean scores at the completion of the research compared to the beginning of the study	84.81	120.7	35.89	1.89[#]
Glycated hemoglobin during study	9.046	8.424	0.6220	109.40[#]
Fasting blood glucose during study	193.5	151.1	42.38	1.60[#]
Postprandial glucose during study	253.2	180.2	73.00	0.93[#]
SBP during study	137.4	130.9	6.470	10.51[#]
DBP during study	83.65	82.09	1.560	43.62[#]

[#]when compared to conventional antidiabetics or standard therapy, empagliflozin had an additional cost to improve the parameter for 3 months of treatment.

DISCUSSION

T2D is significantly raising global burden, particularly in developing nations like India, owing mostly to an increase in the prevalence of overweight/obesity and sedentary lifestyles. T2D was predicted to impact 77 million individuals in India in 2019, with that number expected to rise to more than 134 million by 2045. Approximately 57% of these people remain undiagnosed [15]. T2D is always linked with the age, obesity, diabetes history, smoking, food type and sedentary lifestyle [16]. All around the world including United States, diabetes and its consequences has imposed major financial burden and also its burden may reach 2.2 trillion USD by 2030, accounts upto 2.2 percent global GDP [17]. There are various studies of SGLT-2i which are available for cost effectiveness of empagliflozin as monotherapy, dual or triple therapy or in comparison of people with T2D [18-20]. But the majority of research is relied on data from EMPA-REG trial [8]. In our study, USD 68.05 is also required for empagliflozin 25 mg to be used as an add-on therapy with standard anti-diabetic medication for 3 months. According to our findings, empagliflozin as a new antidiabetic medication will cost USD 109.40, 1.60, 0.93, 10.51, 43.62, and 52.89 to decrease in effectiveness measures, including HbA1C, FBG, PPG, SBP, and DBP, when used as add-on therapy with coventional antidiabetics (Table 3).

In this cost-effectiveness analysis, empagliflozin, a new antidiabetic agent, was shown to be more expensive with a comparably better outcome, requiring additional investigation to establish the likely cost-effectiveness amongst new and conventional antidiabetics. Recent American Diabetes Association recommendations emphasise the importance of "patient-centered" approaches in the care of T2DM patients in terms of their QoL, the avoidance of diabetes complications, and the accomplishment of glycemic targets. As a result, QoL is becoming increasingly important [21]. However, there are few

studies accessible in the Indian context. To the best of our knowledge, this is one of the few studies of treatment methods on the QoL of Indian diabetics. Importantly, to the best of our knowledge, this is the first study in Urdu to utilize the QOLID instrument.

A recent study found no significant association between quality of life and glucose levels in Iranian diabetes patients [22]. In contrast to the Iranian study, our investigation found a favorable connection between glycemic indices and quality of life. As a result, patients demonstrated a substantial increase in quality of life with a drop in FBG, PPG, and HbA1C levels, which is consistent with the findings of this study [23]. According to ICER, the increased cost for one unit more improvement in QOLID score for empagliflozin as a new antidiabetic agent compared to conventional antidiabetics is USD 2.29.

In this cost-effectiveness analysis, empagliflozin, a new antidiabetic agent, was shown to be more expensive with a comparably better outcome, requiring additional investigation to establish the likely cost-effective one among newer and conventional antidiabetics. This was also determined by the ICER study, which demonstrated that novel antidiabetics had a greater additional cost to obtain one unit of health result in terms of efficacy parameters, QOLID, and cost effectiveness when compared to conventional antidiabetics. However, determining whether the additional cost is significant or low is dependent on the country's ICER ceiling value. In India, sufficient information regarding the cost and efficacy of a full menu of programs is lacking; hence, a league table to assess optimal or acceptable ICER value is also lacking. The current study's ICER data may aid in decision-making in the Indian health-care system on an individualized or case-by-case basis, based on socioeconomic status.

CONCLUSION

This study concludes that treatment effectiveness metrics based on quality of life and decreases in efficacy parameters have improved considerably more with empagliflozin as a new antidiabetic compared to conventional antidiabetics. These study findings, may aid in the individualization of type 2 diabetes therapies in the Indian population as a patient centered treatment. This study also demonstrates the synergistic effects of empagliflozin add-on treatment with Metformin (2 g/day), Teneligliptin (20 mg/day), and Glimepiride (8 mg/day) in type 2 diabetes with hypertension.

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