Comparison of Efficacy And Safety Of Vildagliptin And Dapagliflozin In Combination With Metformin In Patients With Type 2 Diabetes Mellitus: A Randomized Open Labeled Parallel Study In Tertiary Care Hospital

Ravinder Singh[1], Sanjana Mehta[1]*, Preetpal Singh[1], Pratima Kumari[1], Suresh Kumar[2], Parminder Nain[3]

[1]Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India

[2]Bharat Institute of Pharmacy, Pehladpur, Babain, Kurukshetra, Haryana, India

[3]Department of Pharmacy Practice, Maharishi Markandeshwar College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Ambala, India

[1]ravi.jaura@gmail.com,*[1]dr.sanjanamehta@gmail.com,[1]preetpal533@gmail.com, [1]pratima.kumari@chitkara.edu.in,[2]drsureshkumarbeniwal@gmail.com, [3]parminder.nain26@gmail.com

Corresponding Author:

*Dr. Sanjana Mehta

Assistant Professor,

Chitkara College of Pharmacy, Chitkara University, Patiala-140401,

Punjab, India.

E-mail: dr.sanjanamehta@gmail.com, sanjana@chitkara.edu.in

ABSTRACT

Aim: The main objective of the study is to compare the efficacy and safety of vildagliptin and dapagliflozin in combination with metformin in Patients with Type 2 Diabetes Mellitus in Tertiary care hospital. Furthermore, the effect of combination drugs on Quality of Life (QOL) was alsoassessed.

Methods: Randomized, open labeled and parallel comparison study was designed and conducted in the out-patient department at Rajindra Hospital, Patiala. The study was held over a period of 4 months from September 2021 to January 2022. The efficacy of the drugs in T2DM was assessed by measuring the glycemic profile of patients such as HbA1C, Fasting Blood Glucose (FBG), Random Blood Glucose (RBG) and anthropometric measures (BMI). However, safety of the drugs was assessed by evaluating the side effects and QOL with the help of SF-36Questionnaire.

Results: Results of the present study have shown that the combination of Group 2 (metformin+ dapagliflozin) has been found more effective in the management of T2DM by reducing HbA1C (10%), Fasting Blood Glucose (26%), Random Blood Glucose (21%), BMI (2.4%) and improving Quality of life of the T2DM patients when compared with Group 1 (metformin+vildagliptin).

Conclusions: The current study's findings reveal that Group 2 (metformin+ dapagliflozin) treatment is more effective and helped in improving Quality of life of T2DM patients than Group 1 (metformin+ vildagliptin) with strict glycemic control in the management of T2DM.

Keywords: Diabetes mellitus; HbA1C; metformin; dapagliflozin; vildagliptin.

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INTRODUCTION

Diabetes mellitus (DM) is a group of chronic metabolic disorders characterized by persistent high blood glucose level (hyperglycemia) with disturbances in metabolic processes such as carbohydrate, fat and protein metabolism

resulting from either due to a lack of insulin synthesis or a failure of the body's cells to respond to insulin effectively, or both. [1] Two major mechanisms for disease pathogenesis have been proposed. Autoimmune destruction of pancreatic β-cells, resulting in insufficient insulin synthesis, as well as endogenous resistance of body cells to insulin action, are the major causes of persistent hyperglycemia associated with diabetes. According to recent statistics by IDF Diabetes Atlas Tenth edition 2021, the prevalence of diabetes has grown dramatically over the last decade and may be termed as developing epidemic. The risk factors for T2DM are a multifaceted combination of genetic, metabolic, and environmental factors that combine to increase the prevalence of the disease. Although there is a substantial genetic basis for individual's predisposition to T2DM due to non- modifiable risk variables (ethnicity and family history/genetic predisposition). The epidemiological studies show that many cases of T2DM can be avoided by reducing the key modifiable risk factors. [4-6] High HbA1c levels in diabetes have recently been recognized as one of the key risk factors for developing micro and macrovascular complications. Dietary treatment can help patients improve their high HbA1c levels, perhaps reducing hyperglycemic complications. It is recommended that diabetes education and awareness should be provided to the people. Diabetes knowledge includes information about dietary habits, exercise, weight monitoring, blood glucose levels, and medication use regarding diabetic complications. Diabetes and its complications can be avoided with effective and active dietary education along with medication. [7] Long-term consequences can be avoided by taking prescribed drugs and leading a healthy lifestyle (i.e., diet and physical activity) Physical activity and exercise training offers a vast array of benefits in addition to glycemic control, including as lowering insulin resistance (IR) and enhancing aerobic capacity, muscle strength, body composition, and endothelial functions. Although exercise improves glycemic control, lipid profile, and other consequences in T2DM, the effectiveness of various types of exercise is less well established. [8, 9] T2DM management is based on a combination of lifestyle changes and pharmacological therapy. Pharmacological therapy includes the oral anti-diabetic agents and injectable insulin.

Vildagliptin is a selective dipeptidyl peptidase-4 (DPP4) inhibitor. It inhibits the breakdown of Incretins by acting on the alpha and beta pancreatic cells. With higher amounts of these chemicals, the islets of Langerhans respond well to aid with glycemic control via insulin regulation and glucagon. When compared to other oral hypoglycemic medications, vildagliptin have potential to reduced incidence of weight gain, hypoglycemia, and peripheral edema. [13] It is used in combination with diet and exercise to help individuals with Type 2 diabetes regulate their blood glucose levels. As a result of this medication, both fasting and post- meal glucose levels are reduced. [14]

Dapagliflozin is another anti-hyperglycemic drug that inhibits the sodium-glucose co-transporter subtype2 (SGLT2). In adults, dapagliflozin improves glycemic management by inhibiting glucose resorption in the proximal tubule of the nephron and inducing glycosuria when used in conjunction with diet and exercise. [15] Dapagliflozin, as monotherapy or in combination with other anti-hyperglycemic drugs, showed excellent glycemic control and decreased bodyweight and blood pressure across a wide range of patients in a number of well-designed clinical trials and their extensions. [16,17] Diabetes is a chronic disease that can have an impact on both health and quality of life (QOL). Several studies have identified certain predictors of QOL in T2DM patients, while their findings were not entirely consistent. QOL is a person's subjective assessment of his or her physical, emotional, and social well-being. Recognizing the QOL predictors and risk factors is crucial since these variables could perhaps be treated for prevention. QOL may be measured using a variety of scales, including the EuroQol 5D (EQ-5D), Audit of Diabetes Dependent Quality of Life (ADDQoL), Diabetes-Specific Quality of Life (DSQL), and Short Form-Series (SF-36, SF-8, SF-12). [18,19]

The 36-Item Short Form Survey (SF-36) is a 36-Item Short Form Health Survey used as part of the Medical Outcomes Study (MOS) designed to explain discrepancies in patient outcomes. The SF-36 is a set of comprehensive, consistent, convenient, reliable and relevant measure for measuring health-related quality of life in adults with a wide range of chronic diseases and in a wide range of countries. [18] It is a multicentre scale with 36 items that is divided into eight

domain profiles of scores: physical functioning (10 items), general health (5 items), role physical (i.e., role limitations due to physical health problems, 4 items), bodily pain (2 items), social functioning (2 items), vitality (4 items), role emotional (i.e., role limitations due to emotional problems, 3 items), and mental health (5 items). A score 0 - 100 was allocated to each domain, with a higher number indicating greater health. [19]. The physical health component comprises of five domains, physical functioning, general health, physical, bodily pain, and vitality. Whereas mental health component also comprises of five domains, social functioning, general health, vitality, role emotional and mental health with two overlapping scales from physical health component. Thus, both physical and mental dimensions have 3 distinct and 2 overlapping scales that signify the scales of vitality and overall health. [20] The goal of this randomized controlled study aimed to investigate the efficacy and safety of combination of Dapagliflozin and Metformin as compared to Vildagliptin and Metformin in combination in patients with T2DM. The primary objective of this randomized controlled study was to determine the most effective pharmacological choice for managing disease progression, with quality of life as secondary outcomes.

Methods

Study Design

The study was designed to compare the efficacy and safety of vildagliptin and dapagliflozin in combination with metformin in patients with type 2 diabetes mellitus in tertiary care hospital. The study has been ethically approved from the Institutional Ethics Committee, Chitkara University, Rajpura. The study was carried out in conformity with the declaration of Helsinki and the code of Good Clinical Practice. The study was held over a period of 4 months from September 2021 to January 2022 including recruiting period. A total of 200 patients were selected as per the inclusion and exclusion criteria. The number of patients during the study remained same before baseline and after 12 weeks. The patients were randomly divided into two groups. The sample size was calculated with the help of Epi info app. After describing the goal and plan of the study, the participants were provided with written consent form in vernacular language for participation in the study. Patients who were recruited were advised that their participation was entirely voluntary and that their refusal would not influence to receive future therapy and the information provided by them will be kept confidential.

Inclusion Criteria

The subjects in the research were belonging to the age group from 40 to 75 years old with the diabetes history of more than 10 years and had uncontrolled type 2 diabetes mellitus with HbA1C levels ≥8% and BMI ≥18 kg/m^2 were included in the study.

Exclusion Criteria

Subjects who are actively taking abusive substances such as alcohol and tobacco were not included in the study. Subject with end stage diseases and history of hospital admission for poor glycemic control (either hyperglycemia or hypoglycemia) within 6 months were also excluded from the study.Patients satisfying the inclusion and exclusion criteria were further randomly divided into 2 groups (100 in each group).

Group 1 Metformin (500mg) + Vildagliptin (50 mg) (BD)

Group 2 Metformin (500 mg) + Dapagliflozin (10 mg) (BD)

After enrollment to the study, glycemic parameters such as HbA1C, Fasting Blood Glucose (FBG), and Random Blood Glucose (RBG) were tested in fully equipped laboratory under supervision of laboratory professional at tertiary care hospital. However, SF-36 questionnaire was used to measure patients' quality of life. Assessment of FBG, RBG and BMI were performed at baseline, after 6 weeks and after 12 weeks of following therapy. However, evaluation of HbA1C and quality of life (QoL) via SF-36 Form were performed at baseline and after12 weeks.

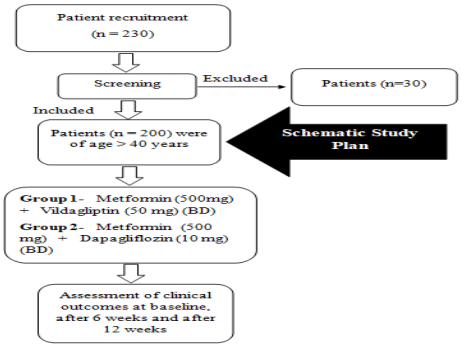

Figure- 1 Schematic study plan

Statistical Analysis

The result data obtained was represented as Mean ± Standard Error of Mean (S.E.M.). The Student t-Test was used to establish a comparison between the two groups. P<0.05 level was considered as statistically significant level of variation among different groups.

Results

Demographics

According to the inclusion and exclusion criteria, 200 patients were included in the research. The patients were randomly divided into two groups; Group 1 and Group 2. A total of 50% patients were of age groups (45-60) years and another 50% patients were of age group (61-75) years. In the participants, 56% subjects were females and 44% subjects were males in both groups. By assessing the BMI of the study population 24% were found to be in normal weight, 40% were overweight and 36% wereobese.

Table 1: Demographic characteristics

S. No.	Variables	Group 1	Group2
1.	**Age (Years)**		
	• **45-60**	52%	48%
	• **61-75**	48%	52%
2.	**Gender (M:F)**		
	• **Male**	36%	52%
	• **Female**	64%	48%
3.	**Duration of Disease (Years)**		
	• **10-15 Years**	64%	56%
	• **16-20 Years**	36%	44%
4.	**BMI**		
	• **18.5 – 24.9 (Normal)**	16%	32%
	• **25 – 29.9 (Overweight)**	52%	28%
	• **≥30 (Obese)**	32%	40%

Effect of Treatments on Glycated Hemoglobin (HbA1C) (%)

After 12 weeks of vildagliptin+metformin therapy to Group 1, there was a change in mean baseline levels of HbA1C from (8.00 ± 0.29) % to (7.60 ± 0.29) % (t = 7.3856, p<0.0001, 95% CI = 0.2868, 0.5092). The reduction in mean HbA1C levels in the Group 1 (vildagliptin+metformin) was significant (p<0.05) when compared to the respective baseline value after 12 weeks of treatment.

After 12 weeks of dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of HbA1C from (8.29 ± 0.32) % to (7.49 ± 0.30) % (t = 19.9481, p<0.0001, 95% CI = 0.7172, 0.8828). The reduction in mean HbA1C levels in the Group 2 (dapagliflozin+metformin) was significant (p<0.05) when compared to the respective baseline value after 12 weeks oftreatment.

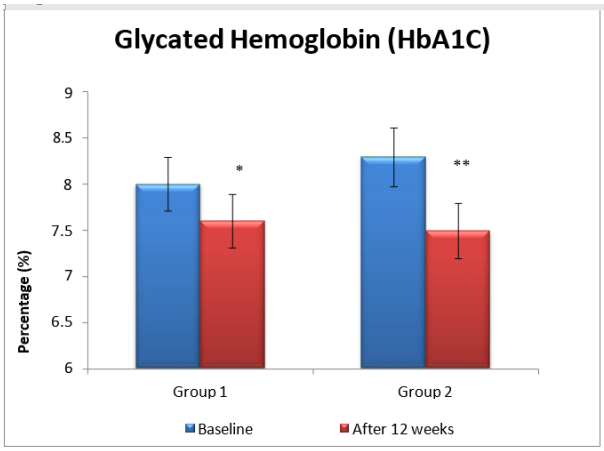

Figure- 2 Effect of Treatments on Glycated Hemoglobin (HbA1C)

(%) Values are expressed as Mean±S.E.M.

***p<0.05 significant when compared Group 1 with baseline data**

****p<0.05 significant when compared Group 2 with Group 1**

Effect of Treatments on Fasting Blood Glucose (mg/dl)

After 6 weeks and 12 weeks of vildagliptin+metformin therapy to Group 1, there was a change in mean baseline levels of FBG from (206.04 ± 15.39) mg/dl to (186.28± 14.36) mg/dl after 6 weeks and (167.05 ± 13.62) mg/dl after 12 weeks, (t = 10.1214, p<0.0001, 95% CI = 31.0445, 46.9483). The reduction in mean FBG levels in the Group 1 (vildagliptin+metformin) was significant (p<0.05) when compared to the respective baseline value after 6 weeks and 12 weeks of treatment.

After 6 weeks and 12 weeks of dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of FBG from (186.64 ± 10.24) mg/dl to (160.48± 8.52) mg/dl after 6 weeks and (137.84 ± 8.05) mg/dl after 12 weeks, (t = 15.9793, p<0.0001, 95% CI = 42.50, 55.10). The reduction in mean FBG levels in the Group 2 (dapagliflozin+metformin) was significant (p<0.05) when compared to the respective baseline value after 6 weeks and 12 weeks of treatment.

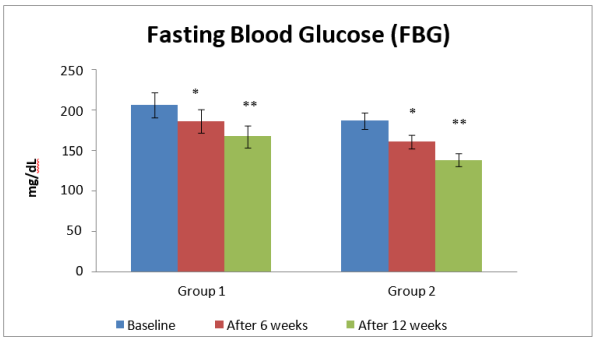

Figure- 3 Effect of Treatments on Fasting Blood Glucose (mg/dl)

Values are expressed as Mean±S.E.M.

***p<0.05 significant when compared Group 1 with baseline data**

****p<0.05 significant when compared Group 2 with Group 1**

Effect of Treatments on Random Blood Glucose (mg/dl)

After 6 weeks and 12 weeks of vildagliptin+ metformin therapy to Group 1, there was a change in mean baseline levels of RBG from (307.3 ± 17.6) mg/dl to (282.7 ± 16.8) mg/dl after 6 weeks and (262.8 ± 16.8) mg/dl after 12 weeks, (t = 7.6582, p<0.0001, 95% CI = 32.46, 56.42). The reduction in mean RBG levels in the Group 1 (vildagliptin+metformin) was significant (p<0.05) when compared to the respective baseline value after 6 weeks and 12 weeks of treatment.

After 6 weeks and 12 weeks of dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of RBG from (300.72 ± 23.00) mg/dl to (266.72 ± 20.79) mg/dl after 6 weeks and (238.40 ± 19.42) mg/dl after 12 weeks, (t = 10.0855, p<0.0001, 95% CI = 49.57, 75.07). The reduction in mean RBG levels in the Group 2 (dapagliflozin+metformin) was significant (p<0.05) when compared to the respective baseline value after 6 weeks and 12 weeks of treatment.

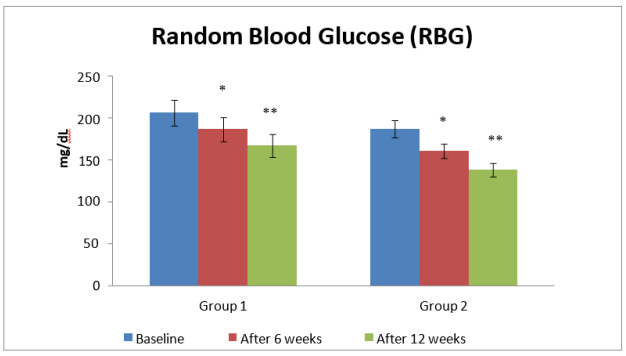

Figure- 4 Effect of Treatments on Random Blood Glucose (mg/dl) Values are expressed as Mean±S.E.M.

***p*<0.05 significant when compared Group 1 with baseline data**

****p*<0.05 significant when compared Group 2 with Group 1**

Effect of Treatments on Anthropometric measures (BMI)

After 6 weeks and 12 weeks of vildagliptin+metformin therapy to Group 1, there was a change in mean baseline levels of BMI from (28.44 ± 0.80) kg/m^2 to (28.20 ± 0.79) kg/m^2 after 6 weeks and (27.93 ± 0.79) kg/m^2 after 12 weeks, (t = 20.3111, p<0.0001, 95% CI = 0.4578, 0.5614). The reduction in mean BMI levels in the Group 1 (vildagliptin+metformin) was significant (p<0.05) when compared to the respective baseline value after 6 weeks and 12 weeks of treatment.

After 6 weeks and 12 weeks of dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of (28.27 ± 0.94) kg/m^2 to (27.92 ± 0.94) kg/m^2 after 6 weeks and (27.58 ± 0.94) kg/m^2 after 12 weeks, (t = 32.4180, p<0.0001, 95% CI = 0.6491, 0.7373). The reduction in mean BMI levels in the Group 2 (dapagliflozin+metformin) was significant (p<0.05) when compared to the respective baseline value after 6 weeks and 12 weeks oftreatment.

Effect of Treatments on QOL on the Basis of 36-Item Short Form Survey (SF- 36):

Effect of Treatments on Physical Component Summary (PCS)

After 12 weeks of vildagliptin+metformin therapy to Group 1, there was a change in mean baseline levels of PCS from (41.69 ± 1.15) to (49.07 ± 1.05) (t = 4.7289, p<0.0001, 95% CI =-10.5167, -4.2417). The increase in mean PCS levels in the Group 1 (vildagliptin+metformin) was significant (p<0.05) when compared to the respective baseline value after 12 weeks of treatment.

After 12 weeks of dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of PCS from (44.51 ± 1.14) to (51.96 ± 0.83) (t = 5.2623, p<0.0001, 95% CI = -10.30618, -4.60782). The increase in mean PCS levels in the Group 2 (dapagliflozin + metformin) was significant (p<0.05) when compared to the respective baseline value after 12 weeks of treatment.

Effect of Treatments on Mental Component Summary (MCS)

After 12 weeks of vildagliptin+metformin therapy to Group 1 , there was a change in mean baseline levels of MCS from (35.79 ± 1.99) to (44.42 ± 1.51) (t = 3.4466, p<0.0012, 95% CI= -13.6696, -3.5968). The increase in mean MCS levels in the Group 1 (vildagliptin+metformin) was significant (p<0.05) when compared to the respective baseline value after 12 weeks of treatment.

After 12 weeks of dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of MCS from (41 ± 1.51) to (49.17 ± 1.20) (t = 4.2237, p<0.0001, 95% CI = -12.06304, -4.28208). The increase in mean MCS levels in the Group 2 (dapagliflozin+metformin) was significant (p<0.05) when compared to the respective baseline value after 12 weeks of treatment.

Table 2: Effect of Treatments on Quality of Life

	PCS		MCS	
	Pre	**Post**	**Pre**	**Post**
Group 1	41.69 ± 1.15	49.07 ± 1.05	35.79 ± 1.99	44.42 ± 1.51
Group 2	44.51 ± 1.14	51.96 ± 0.83	41 ± 1.51	1.20

Effect of Treatments on Safety Parameters

The side effects were observed in the study population, frequency of occurrence of side effects in 24 % of the patients in the treatment

Group 1 and in the 16 % of the patients in the treatment Group 2.

Table 3: Table showing effect of treatment on safety parameters

Side Effects	Group 1	Group 2
	Frequency of Occurrence (%)	Frequency of Occurrence (%)
Dizziness	8	4
Urinary Tract Infections	0	8
Nausea	16	12
Diarrhea	8	4
Weakness	20	12
Body Pain	16	8
Headache	8	4

Discussions

A total of 200 patients were selected as per the inclusion and exclusion criteria. The patients were randomly divided into two groups; Group 1 and Group 2. Almost 50% patients were of age groups (45-60) years and another 50% patients were of age group (61-75) years. T2DM is extremely variable in older adults, but it is often associated with varying degrees of underlying insulin resistance (IR), excessive adiposity, and β-cell dysfunction. Another study suggests that older adults of ≥65 years of age with T2DM account for approximately half of all diabetes patients. [21] In the study participants, 56% subjects were females and 44% subjects were males in both groups. Diabetes is more common in males than in women, especially in middle-aged populations, with the exception of specific regions of the world, such as the Middle East and North Africa. [22] By assessing the BMI of the study population 24% were found to be normal weight, 40% were overweight and 36% were obese. According to a study, there is a link between type 2 diabetes and obesity as assessed by BMI, with the prevalence of type 2 diabetes growing considerably only in ≥ 45 years old with a BMI of 30 kg/m^2.[23]

The glycemic parameters such as HbA1C, FBG and RBG were analyzed to assess the efficacy of the drugs. After 12 weeks of vildagliptin+metformin therapy to Group 1 and dapagliflozin+metformin therapy to Group 2, there was a change in baseline levels of HbA1C i.e., 5% and 10% respectively. Group 2 (dapagliflozin+metformin)was found to be more effective in reducing HbA1C than the Group 1 (vildagliptin+metformin). High HbA1c levels in diabetes have recently been recognized as one of the key risk factors for developing micro and macrovascular complications. [7]

After 6 weeks of vildagliptin + metformin therapy to Group 1 and dapagliflozin+metformin therapy to Group 2, there was a change in baseline levels of FBG i.e., 10% and 14% respectively. After 12 weeks of vildagliptin+metformin therapy to Group 1 and dapagliflozin+metformin therapy to Group 2, there was a change in baseline levels of FBG i.e., 19% and 26% respectively. Group 2 (dapagliflozin+metformin) was found to be more effective in reducing FBG than the Group 1(vildagliptin+metformin). [14]

After 6 weeks of vildagliptin+metformin therapy to Group 1 and dapagliflozin+metformin therapy to Group 2, there was a change in baseline levels of RBG i.e., 8% and 11% respectively. After 12 weeks of vildagliptin+metformin therapy to Group 1 and dapagliflozin+metformin therapy to Group 2, there was a change in mean baseline levels of RBG i.e., 14% and 21% respectively. Group 2 (dapagliflozin+metformin) was found to be more effective in reducing RBG than the Group 1(vildagliptin+metformin). [15]

Diabetes can impair mood and self-esteem, causing frustration and symptoms associated with depression; additionally, food limitations and comorbidities in sexual life can lead to disputes and severely impact the patient's QOL. In recent years, quality of life (QoL) has received a lot of attention as a key health-care outcome. Medicine should strive to preserve and restore both the patient's health and dignity. QoL is defined as a sense of well-being that includes physical, psychological, social, and spiritual well-being. When we discuss regarding QoL in patients with chronic conditions, we can describe it as the total assessment of the subject's life, which is influenced by both the subject's features and external factors.

The epidemiological profile and characteristics related with QOL in patients could help to build a complete program that includes interventions for

effective self-care, encouragement of proper medication use, and maintenance of healthy collective and individual conditions. [16]The 36-Item Short Form Survey (SF-36) is a 36-Item Short Form Health Survey used as part of the Medical Outcomes Study (MOS) designed to explain discrepancies in patient outcomes. The SF-36 is a set of comprehensive, consistent, and convenientquality-of-life indicators. These self-reporting indicators are now widely employed by managed care organization and Healthcare for daily monitoring and evaluation of adult patient care outcomes. [18]

Initially after the enrollment of patients the QOL of patients were assessed using SF- 36 Form. In Group 1, 92% patients were having poor QOL and 8% patients were having moderate QOL while in Group 2, 84% patients were having poor QOL and 16% patients were having moderate QOL. After 12 weeks of vildagliptin+metformin therapy to Group 1 and dapagliflozin+metformin therapy to Group 2, there was a significant improvement i.e., In Group 1, 56% patients were having poor QOL and 44% patients were having moderate QOL while in Group 2, 36% patients were having poor QOL and 64% patients were having moderate QOL.

Conclusion: Results of the present study have shown that the combination of Group 2 (metformin+dapagliflozin) has been found more effective in the management of T2DM by reducing HbA1C (10%), Fasting Blood Glucose (26%) and Random Blood Glucose (21%) when compared with Group 1 (metformin+vildagliptin). Outcome of the present study revealed a significant decrease in HbA1C, BMI, FBG and RBG with combination of Metformin + Dapagliflozin as compared with Metformin + Vildagliptin. This reflects that when Dapagliflozin was given in combination with Metformin there is greater reduction in HbA1C, BMI, FBG and RBG as compared to Vildagliptin in combination with metformin.By analyzing the interviews, physical examination and laboratory investigations we concluded that these drugs were well tolerated and patient showed full compliance towards the treatment during the study. Furthermore, the quality of life (QOL) of patients was significantly improved by successfully following the treatment during the period of study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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