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Impact of Dapagliflozin as Add-on Therapy on Glycemic Status and Quality of Life in Type 2 Diabetic Patients

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ABSTRACT

To evaluate the efficacy of Dapagliflozin as add-on therapy on glycaemic and obesity parameters in type 2 diabetes patients (T2DM) with inadequate glycaemic control and the reflection of this effect on the patient's quality of life (QoL). Methods: Patients with uncontrolled T2DM [Haemoglobin A1c 7.0%-12.0%] on sulfonylurea, metformin, and gliptin were selected to receive Dapagliflozin 5mg/day for 16 weeks (n=40). Fasting and postprandial plasma glucose, glycated hemoglobin A1c, body weight, and waist circumference were measured. Assessment of patients' QoL was performed using the Quality of Life Scale for Iraqi Diabetic patients (QOLSID) at baseline and after administration of Dapagliflozin. Dapagliflozin showed a significant reduction in fasting and postprandial plasma glucose, glycated hemoglobin A1c (HbA1c), body mass index (BMI), and index of central obesity (ICO) ($p<0.001$). A significant change in the QOLSID score was also detected after treatment ($p<0.001$). High BMI was a negative predictor for patients' QoL. Dapagliflozin achieved beneficial effects on Iraqi T2DM patients who were already inadequately controlled by three oral antidiabetic agents. This promising result may help physicians in prescribing Dapagliflozin as an alternative to insulin for patients who refuse injectable anti-diabetic agents.

Keywords: Type 2 DM, Dapagliflozin, Haemoglobin A1c, Quality of life

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a syndrome of metabolic dysregulation that needs multifactorial behavioral and pharmacological treatments to prevent or delay complications, morbidity, and mortality. Uncontrolled hyperglycemia can negatively affect the patient's physical and psychological status and thus lower the patient's quality of life (QoL) (Verma & Dadarwal, 2017) (Vanstone *et al*., 2015) (Gebremedhin *et al*., 2019). According to American Diabetes Association (ADA), when hyperglycemia remains uncontrolled (HbA1c ≥1.5% above the glycemic target), a second therapy for T2DM is needed (Davies *et al*., 2022).

It has been ascertained by ADA, besides the glucose-lowering effect the add-on antidiabetic medication should have an impact on weight management to achieve and maintain the optimum glycemic and weight control which are the goals in people without established cardiorenal risks (Vijan *et al*., 2014) (Inzucchi *et al*., 2012). Although metformin is still the first-line pharmacotherapy in most T2DM patients, according to the American Diabetes Association (ADA) (Association, 2020) but has little or even weight weight-neutral effect, as well as gliptins (Hermansen & Mortensen, 2007) *(Sazan et al*., 2012). Other old antidiabetic classes such as thiazolidinediones (TZDs) and sulfonylureas (SUs) in spite of their efficacy in controlling glycemia but their use is associated with weight gain and other adverse effects (Derosa & Maffioli, 2010) (Najim *et al*., 2014) (Fonseca, 2003). However, the newest class of antidiabetic drugs, sodium-glucose cotransporter 2 inhibitors (SGLT2i), are approved for the treatment of T2DM as an add-on or even initial therapy (Tamez-Pérez *et al*., 2013). This class acts by inducing glycosuria and thus improving glycemic status without affecting insulin levels (Merovci *et al*., 2015). Dapagliflozin is a highly selective inhibitor of SGLT2. It has been well tolerated and its safety and

efficacy approved in clinical trials, mostly on cardio-renal outcomes with additional benefits of weight loss and low risk of hypoglycemia (Heerspink *et al*., 2020) (Solomon *et al*., 2022) (Wiviott *et al*., 2019) (McMurray *et al*., 2019). To date, no clinical data regarding SGLT2i recorded in Iraqi patients with limited data available on the Arabic population. On Qatari, an assessment of Dapagliflozin effectiveness revealed a significant improvement in the glycemic status after 6 months when used in combination with standard therapy, a reduction (Al AdAwi *et al*., 2019). In Saudi Arabia, Dapagliflozin was found to be a well-tolerated and effective treatment option for T2DM patients after 6 months (Alguwaihes, 2021).

Current orientation towards Quality of Life (QoL) measures means that patients' opinions on the effects of healthcare and medical interventions on their lives can now be evaluated and considered in clinical decision-making (Addington-Hall & Kalra, 2001). Thus, to determine the effectiveness of any new treatment for T2DM patients, it is necessary to assess the improvement in both glycemic control and the patient's QoL (Ishii *et al*., 2017) (Aso *et al*., 2017) (Mostafa *et al*., 2018).

This study aimed to evaluate the impact of Dapagliflozin on glycemic control, obesity parameters, and QoL for a sample of Iraqi T2DM patients already treated with oral antidiabetic agents (OADs) in Baghdad.

MATERIAL AND METHODS

Study Design

This interventional randomized clinical study was conducted from May to December 2022, at the National Diabetic Centre for Treatment and Research/ Mustansiriyah University/ Baghdad/ Iraq. Ethical approval from the diabetic center and college of Pharmacy/ Mustansiriyah University was taken before the study initiation. All investigations/ procedures carried out in this study involving human participants were in accordance with the 1975 Declaration of Helsinki and its later amendments.

Participants Recruitment

Patients enrolled in the study with the following criteria: T2DM patients, aged between 18-70 years, on a combination of OADs (sulfonylurea + metformin + gliptin) for at least 8 weeks before enrolment. Patients involved had elevated glycosylated hemoglobin A1c (HbA1c) [7%-12.0%] at the time of enrollment. Patients who met the inclusion criteria and agreed to the study protocol were recruited; written consent was obtained from all participants before starting the study. All patients involved received Dapagliflozin 5mg daily for 16 weeks. Sulfonylurea could be down-titrated only once during the treatment period to mitigate the risk of recurrent hypoglycemic events at the discretion of the investigator. Initially, 45 participants met the criteria involved in the study and finished all the baseline requirements. At the end of the study, five cases were recruited and the most with the most common reasons for discontinuation were non-adherent with the study medication (1 case), non-compliance with the appointment (2 cases), and adverse events (2 cases of genitourinary infection). A total of 40 patients completed the study.

Data collection

The participants were interviewed and their sociodemographic and clinical data (medication history, disease history, and diabetes-related information) were collected.

Outcome Measures

The study's outcomes measured the changes pre-and post-treatment with Dapagliflozin (week 0 to week 16). The following parameters being measured: HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG; glucose level measured 2 hours after standardized breakfast), body weight (BW), height (Ht), waist circumference (WC), body mass index (BMI), index of central obesity (ICO), and patients' QoL.

Quality of Life Assessment Tool

The QOLSID tool, introduced in 2020 by Mikhael EM *et al*. (Mikhael *et al*., 2020), was used in this study to measure the QoL in T2DM. The questionnaire consisted of 10 questions with 5 likert scale answers ranging from (0-4). Scores more than 32.5 indicate a good quality of life. The Arabic version of the QOLSID was administered to the participants at baseline (week 0) and after 16 weeks.

Statistical Analysis

Statistical analysis was performed using SPSS (Version 29) and Microsoft Excel (2010). After testing the normality of distribution for the studied parameters, Paired Samples T-test was performed for comparison between pre-and post-treatment values. Bivariate correlation was performed to identify the correlations with QoL. Comparison between patients' groups was performed with Independent T-test. A p-value of <0.05 was considered significantly different.

Table I. Patients' demographic and disease characteristics

Demographic Characters			**No (%)**
Age (years)	≤60		31 (77.5)
	>60		9 (22.5)
Gender	Male		18 (45)
	Female		22 (55)
BMI (kg/m2)	25 - 29.9		14 (35)
	30 - 34.9		12 (30)
	≥ 35		14 (35)
WC (cm)	Male	≥ 94	18 (45)
	Female	≥ 80	22 (55)
Smoking	Yes		10 (25)
	No		30 (75)
Alcohol	Yes		4 (10)
	No		36 (90)
Educational level	Illiterate		8 (20)
	Primary		3 (7.5)
	Secondary		16 (40)
	College		13 (32.5)
Residence	Urban		28 (70)
	Rural		12 (30)
Monthly Income ($)	<500		14 (35)
	500-1000		26 (65)
Duration of T2DM (years)	<5		8 (20)
	5-10		10 (25)
	≥10		22 (55)
Family History of T2DM	Yes		32 (80)
	No		8 (20)
Medical history	Non		23 (57.5)
	Comorbid disease		17 (42.5)

Data presented as number and percentage.

RESULTS AND DISCUSSION

Patients' demographic and disease characteristics are summarized in (Table I). Patients using Dapagliflozin, for 16 weeks, demonstrated a high significant reduction in FPG, PPG, HbA_{1c}, BMI, and WC (p<0.001). Moreover, ICO was significantly reduced (p<0.05) (Table II).

Quality of Life Scale for Iraqi DM patients (QOLSID)

There was a significant change (p<0.001) in the QOLSID total score after 16 weeks of treatment with Dapagliflozin. In the majority of the patients, Dapagliflozin showed a significant improvement in the patient's satisfaction with the diet, ability to exercise, night sleep, and stress due to daily blood glucose testing (p<0.001). Dapagliflozin also showed significant improvement in the personal ability to control blood glucose and most patients were more satisfied about their overall health after adding Dapagliflozin to their treatment (p<0.05). There was an increase in satisfaction regarding the effect of Dapagliflozin as well as a decrease in the anxiety from their disease but these were non-significant (p>0.05). Some items were significantly correlated with the total QOLSID score more than others (p<0.01) (Table III).

Based on the results of statistical analysis, QOLSID score not affected by demographic or disease characteristics (p≥0.05) (Table IV).

Factors Affecting Quality of Life removed.

This is the first follow-up study on Iraqis to explore the efficacy of Dapagliflozin in T2DM patients who are inadequately controlled by a combination of OADs.

Table II. Laboratory values change from baseline (at weeks 0 and 16).

Variables	Baseline	After 16 weeks	% of change	P-Value [a]
FPG (mg/dl)	235.68 ± 75.30	159.20 ± 19.12	-32.4	0.001**
PPG (mg/dl)	281.49 ± 127.79	195.83 ± 69.24	-30.4	<0.001**
HbA1c (%)	9.65 ± 2.06	7.99 ± 1.31	-17.2	<0.001**
BW (kg)	85.85 ± 13.84	83.87 ± 14.46	-2.3	0.002**
Ht (cm)	165.2 ± 10.64	-	-	-
BMI (mg/m2)	34.93 ± 4.31	33.73 ± 4.33	-3.4	<0.001**
WC (cm)	112.93 ± 7.42	109.93 ± 7.52	-2.7	<0.01**
ICO	0.68 ± 0.17	0.67 ± 0.16	-1.5	0.01*

Data presented as mean ± SD, [a] Paired Samples T-test used for comparison between pre- and post-treatment, (*) significant changes (p<0.05), (**) highly significant changes (p<0.01).

Table III. Effect of Dapagliflozin on Quality of Life (QOLSID)

Questions	Pre-treatment	Post-treatment [b]	p-value [a]
Q1 Satisfied with diet restriction required to control your diabetes?	2.27 ± 1.35	3.27 ± 0.83**	<0.001**
Q2 Satisfied with your current diabetes treatment?	2.68 ± 0.95	3.00 ± 0.98**	0.167
Q3 Satisfied with your ability to do an exercise (e.g. brisk walking, cycling or swimming)?	1.77 ± 1.34	3.00 ± 0.82*	<0.001**
Q4 Satisfied with your ability to control diabetes?	1.95 ± 1.25	2.50 ± 0.96**	0.03*
Q5 Satisfied with health care services that you receive?	3.13 ± 0.94	3.45 ± 0.74**	0.069
Q6 Feeling stressed by blood glucose testing?	1.91 ± 1.54	3.23 ± 0.75**	<0.001**
Q7 Feeling stressed or anxious to diabetes?	3.00 ± 1.11	3.32 ± 0.78	0.148
Q8 Satisfied with the support you get from your friends and family?	3.00 ± 1.07	3.23 ± 0.84	0.071
Q9 Satisfied with your night sleep?	1.86 ± 1.21	2.95 ± 0.65**	<0.001**
Q10 Satisfied with your overall health?	1.86 ± 1.58	2.59 ± 1.26**	0.02*
Total score	**24.45 ± 5.76**	**31.09 ± 3.66**	**<0.001****

Data presented as mean ± SD, [a] Paired Samples T-test used for comparison between pre- and post-treatment, [b] Correlation coefficient used to correlate the items with total score, (*) significant changes (p<0.05), (**) highly significant changes (p<0.01).

It has been demonstrated by a previous study on Korean that the addition of Dapagliflozin as add-on therapy in T2DM patients already on a triple OADs suffering from inadequate glycemic control could be an effective and safe alternative treatment to insulin injection (Jeon *et al*., 2018). Because the mechanism of action of Dapagliflozin does not depend upon existing β-cell function, thus making it a suitable agent in the management of patients not at goal with ongoing therapy.

In the present study, Dapagliflozin 5mg/day as add-on therapy significantly improved glycemic status and weight indices consistent with previous studies (Matthaei *et al*., 2015) (Bolinder *et al*., 2014) (Jabbour *et al*., 2014) (Matthaei *et al*., 2015). Dapagliflozin significantly reduced both fasting and postprandial hyperglycemia, which are important to achieve optimal glucose control and to prevent microvascular and macrovascular complications, as it has been confirmed the role of postprandial hyperglycemia with the development of long-term complications, cardiovascular morbidity and mortality in T2DM (Heine *et al*., 2004) (Monnier *et al*., 2007). In addition, postprandial hyperglycemia was found to influence HbA1c more and faster than fasting hyperglycemia when HbA1c levels approach target values (Faruqui, 2017). Regarding obesity parameters, Dapagliflozin significantly reduced body weight, waist circumference, and consequently BMI besides ICO within 16 weeks.

Table IV. Association of demographic and disease characteristics with QOLSID after treatment with Dapagliflozin

Demographic and disease characters		QOLSID	p-value[a]
Age	≤60	30.48 ± 4.54	**0.291** **NS**
	>60	32.38 ± 4.03	
Gender	Male	30.47 ± 4.68	**0.546** **NS**
	Female	31.33 ± 4.23	
BMI	25 - 29.9	32.46 ± 2.60	**0.162** **NS**
	30 - 34.9	29.08 ± 4.59	
	35 – 39.9	30.56 ± 2.55	
	≥40	30.40 ± 5.27	
Waist Circumference	Male ≥ 94	30.63 ± 4.44	**0.990** **NS**
	Female ≥ 80	30.61 ± 3.51	
Educational Level	Illiterate	31.63 ± 3.20	**0.816** **NS**
	Primary	31.33 ± 2.89	
	Secondary	30.06 ± 4.34	
	College	30.69 ± 3.95	
Monthly Income	<500	29.80 ± 4.03	**0.151** **NS**
	500-1000	31.55 ± 3.50	
Family History	Yes	31.09 ± 3.74	**0.169** **NS**
	No	29.00 ± 3.96	
Duration of DM	<5	32.71 ± 1.70	**0.249** **NS**
	5-10	33.50 ± 2.87	
	≥10	29.86 ± 4.62	

Data presented as mean ± SD, [a] Independent t-test used to test statistical differences between groups. NS: No significant changes (p≥0.05).

This reduction represents a potentially beneficial effect of Dapagliflozin as add-on therapy. The mechanism by which Dapagliflozin induces weight reduction may relate to caloric loss due to sustained elevation in urinary glucose excretion leading to fat loss, osmotic diuresis, or a combination of both factors (Bolinder *et al*., 2012).

The present study evaluated the patients' QOL upon the addition of Dapagliflozin. The study results in this regard found a significant improvement in several QOL aspects after adding Dapagliflozin therapy not related to demographic or disease characteristics, indicating that improvement in glycemic status plays the main role. It is well known that DM has a negative impact on patient's physical, social and mental state. Persistent hyperglycemia despite taking multiple OADs adds an extra burden on the patient's QOL (Prajapati *et al*., 2018) (Kalra *et al*., 2018). Therefore, the above finding was extremely reasonable, since Dapagliflozin significantly improved glycemic control, thus reducing anxiety and improving patients' psychological condition and finally improved overall QOL.

Body weight improvement with Dapagliflozin is consistently associated with improvement in QOL in the present study. It is well known that obesity is the stronger risk factor for T2DM and is associated with metabolic abnormalities resulting from insulin resistance (Bellou *et al*., 2018) (Galicia-Garcia *et al*., 2020). Also, weight loss remains the cornerstone therapy to improve insulin sensitivity and, in some circumstances, to prevent the incidence of T2DM in obese individuals (Galicia-Garcia *et al*., 2020). Thus, we confirm the beneficial effects of Dapagliflozin on the glycemic status of T2DM either directly or through improving body weight control. This is consistent with two randomized controlled trials that evaluated the effect of Dapagliflozin 10mg as add-on to metformin in T2DM for 24 weeks, Dapagliflozin-induced weight loss was associated with improvement in overall health-related quality of life (HRQOL) (Grandy *et al*., 2014) (Grandy *et al*., 2014). Another randomized controlled trial on Japanese for 24 weeks compared the effect of Dapagliflozin 5mg against Dipeptidyl Peptidase 4 Inhibitors (DPP4i) in drug-naïve T2DM patients,

Dapagliflozin significantly reduced body weight and showed more favorable benefit on patients' QOL (Ishii *et al*., 2020). modified

The study had the following limitations. The small sample size, as this is the first study on Dapagliflozin as add-on to three OADs in Iraqi patients. Therefore, the current study could be considered as a pilot study and thus it is highly recommended to conduct another study on a larger sample to confirm the current study findings. The study was conducted on a sample of Iraqi patients which could potentially limit the generalizability of the findings to diabetic patients in other countries.

CONCLUSION

The usage of Dapagliflozin as add-on therapy to Iraqi T2DM patients who were already on three OADs resulted in better glycemic control, a reduction in BMI, and an improvement in QOL.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Addington-Hall, J., & Kalra, L. (2001). Who Should Measure Quality of Life? *BMJ (Clinical Research Ed.)*, *322*(7299), 1417–1420. https://doi.org/10.1136/bmj.322.7299.1417

Al AdAwi, R. M., Jassim, Z., Elgaily, D., Abdelaziz, H., Sree, B., & Mohamed Ibrahim, M. I. (2019). Assessment of Dapagliflozin Effectiveness as Add-on Therapy for the Treatment of Type 2 Diabetes Mellitus in a Qatari Population. *Scientific Reports*, *9*(1), 6864. https://doi.org/10.1038/s41598-019-43052-6

Alguwaihes, A. M. (2021). Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus in Saudi Arabia: A Post Authorization Safety Study. *Diabetes Therapy : Research, Treatment and Education of Diabetes and Related Disorders*, *12*(7), 1979–1992. https://doi.org/10.1007/s13300-021-01092-0

Aso, Y., Suzuki, K., Chiba, Y., Sato, M., Fujita, N., Takada, Y., Murano, S., & Kuroda, H. (2017). Effect of Insulin Degludec versus Insulin Glargine on Glycemic Control and Daily Fasting Blood Glucose Variability in Insulin-naïve Japanese Patients with Type 2 Diabetes: I'D GOT trial. *Diabetes Research and Clinical Practice*, *130*, 237–243. https://doi.org/10.1016/j.diabres.2017.06.007

Association, A. D. (2020). Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care*, *43*(Suppl 1), S98–S110. https://doi.org/10.2337/dc20-S009

Bellou, V., Belbasis, L., Tzoulaki, I., & Evangelou, E. (2018). Risk Factors for Type 2 Diabetes Mellitus: an Exposure-wide Umbrella Review of Meta-analyses. *PloS One*, *13*(3), e0194127.

Bolinder, J., Ljunggren, Ö., Johansson, L., Wilding, J., Langkilde, A. M., Sjöström, C. D., Sugg, J., & Parikh, S. (2014). Dapagliflozin Maintains Glycaemic Control while Reducing Weight and Body Fat Mass over 2 Years in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin. *Diabetes, Obesity and Metabolism*, *16*(2), 159–169. https://doi.org/https://doi.org/10.1111/dom.12189

Bolinder, J., Ljunggren, Ö., Kullberg, J., Johansson, L., Wilding, J., Langkilde, A. M., Sugg, J., & Parikh, S. (2012). Effects of Dapagliflozin on Body Weight, Total Fat Mass, and Regional Adipose Tissue Distribution in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin. *The Journal of Clinical Endocrinology & Metabolism*, *97*(3), 1020–1031. https://doi.org/10.1210/jc.2011-2260

Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., Rosas, S. E., Del Prato, S., Mathieu, C., Mingrone, G., Rossing, P., Tankova, T., Tsapas, A., & Buse, J. B. (2022). Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, *45*(11), 2753–2786. https://doi.org/10.2337/dci22-0034

Derosa, G., & Maffioli, P. (2010). Effects of Thiazolidinediones and Sulfonylureas in Patients with Diabetes. *Diabetes Technology & Therapeutics*, *12*(6), 491–501.

Faruqui, A. (2017). *Post Prandial Hyperglycemia: A Real Threat for Patients with Type 2 Diabetes Mellitus*.

Fonseca, V. (2003). Effect of Tiazolidinediones on Body Weight in Patients with Diabetes Mellitus. *The American Journal of Medicine*, *115*(8, Supplement 1), 42–48. https://doi.org/https://doi.org/10.1016/j.amjmed.2003.09.005

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, *21*(17). https://doi.org/10.3390/ijms21176275

Gebremedhin, T., Workicho, A., & Angaw, D. A. (2019). Health-related Quality of Life and Its Associated Factors among Adult Patients with Type II Diabetes Attending Mizan Tepi University Teaching Hospital, Southwest Ethiopia. *BMJ Open Diabetes Research and Care*, *7*(1), e000577.

Grandy, S., Hashemi, M., Langkilde, A.-M., Parikh, S., & Sjöström, C. D. (2014). Changes in Weight Loss-related Quality of Life among Type 2 Diabetes Mellitus Patients Treated with Dapagliflozin. *Diabetes, Obesity and Metabolism*, *16*(7), 645–650. https://doi.org/https://doi.org/10.1111/dom.12263

Grandy, S., Langkilde, A. M., Sugg, J. E., Parikh, S., & Sjöström, C. D. (2014). Health-related Quality of Life (EQ-5D) among Type 2 Diabetes Mellitus Patients Treated with Dapagliflozin over 2 years. *International Journal of Clinical Practice*, *68*(4), 486–494. https://doi.org/https://doi.org/10.1111/ijcp.12341

Heerspink, H. J. L., Stefánsson, B. V., Correa-Rotter, R., Chertow, G. M., Greene, T., Hou, F.-F., Mann, J. F. E., McMurray, J. J. V., Lindberg, M., Rossing, P., Sjöström, C. D., Toto, R. D., Langkilde, A.-M., & Wheeler, D. C. (2020). Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*, *383*(15), 1436–1446. https://doi.org/10.1056/nejmoa2024816

Heine, R. J., Balkau, B., Ceriello, A., Del Prato, S., Horton, E. S., & Taskinen, M.-R. (2004). What does Postprandial Hyperglycaemia Mean? *Diabetic Medicine : A Journal of the British Diabetic Association*, *21*(3), 208–213. https://doi.org/10.1111/j.1464-5491.2004.01149.x

Hermansen, K., & Mortensen, L. S. (2007). Bodyweight Changes Associated with Antihyperglycaemic Agents in Type 2 Diabetes Mellitus. *Drug Safety*, *30*, 1127–1142.

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., Peters, A. L., Tsapas, A., Wender, R., & Matthews, D. R. (2012). Management of Hyperglycaemia in Type 2 Diabetes: a Patient-centered Approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*, *55*(6), 1577–1596. https://doi.org/10.1007/s00125-012-2534-0

Ishii, H., Nakajima, H., Kamei, N., Niiya, T., Hiyoshi, T., Hiramori, Y., Ohtsu, S., Noto, T., & Shimono, D. (2020). Quality-of-Life Comparison of Dapagliflozin Versus Dipeptidyl Peptidase 4 Inhibitors in Patients with Type 2 Diabetes Mellitus: A Randomized Controlled Trial (J-BOND Study). *Diabetes Therapy : Research, Treatment and Education of Diabetes and Related Disorders*, *11*(12), 2959–2977. https://doi.org/10.1007/s13300-020-00941-8

Ishii, H., Niiya, T., Ono, Y., Inaba, N., Jinnouchi, H., & Watada, H. (2017). Improvement of Quality of Life through Glycemic Control by Liraglutide, a GLP-1 Analog, in Insulin-naive Patients with Type 2 Diabetes Mellitus: the PAGE1 study. *Diabetology & Metabolic Syndrome*, *9*, 3. https://doi.org/10.1186/s13098-016-0202-0

Jabbour, S. A., Hardy, E., Sugg, J., Parikh Shamik, & Group, for the S. 10. (2014). Dapagliflozin Is Effective as Add-on Therapy to Sitagliptin with or Without Metformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. *Diabetes Care*, *37*(3), 740–750. https://doi.org/10.2337/dc13-0467

Jeon, H. J., Ku, E. J., & Oh, T. K. (2018). Dapagliflozin Improves Blood Glucose in Diabetes on Triple Oral Hypoglycemic Agents Having Inadequate Glucose Control. *Diabetes Research and Clinical Practice*, *142*, 188–194. https://doi.org/https://doi.org/10.1016/j.diabres.2018.05.013

Kalra, S., Jena, B. N., & Yeravdekar, R. (2018).

Emotional and Psychological Needs of People with Diabetes. *Indian Journal of Endocrinology and Metabolism*, *22*(5), 696.

Matthaei, S., Bowering, K., Rohwedder, K., Grohl, A., Parikh, S., & Group, for the S. 05. (2015). Dapagliflozin Improves Glycemic Control and Reduces Body Weight as Add-on Therapy to Metformin Plus Sulfonylurea: A 24-Week Randomized, Double-Blind Clinical Trial. *Diabetes Care*, *38*(3), 365–372. https://doi.org/10.2337/dc14-0666

Matthaei, S., Bowering, K., Rohwedder, K., Sugg, J., Parikh, S., & Johnsson, E. (2015). Durability and Tolerability of Dapagliflozin over 52 weeks as Add-on to Metformin and Sulphonylurea in Type 2 Diabetes. *Diabetes, Obesity & Metabolism*, *17*(11), 1075–1084. https://doi.org/10.1111/dom.12543

McMurray, J. J. V, Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., Ponikowski, P., Sabatine, M. S., Anand, I. S., & Bělohlávek, J. (2019). Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*, *381*(21), 1995–2008.

Merovci, A., Mari, A., Solis-Herrera, C., Xiong, J., Daniele, G., Chavez-Velazquez, A., Tripathy, D., Urban McCarthy, S., Abdul-Ghani, M., & DeFronzo, R. A. (2015). Dapagliflozin Lowers Plasma Glucose Concentration and Improves β-cell Function. *The Journal of Clinical Endocrinology and Metabolism*, *100*(5), 1927–1932. https://doi.org/10.1210/jc.2014-3472

Mikhael, E. M., Hassali, M. A., Hussain, S. A., & Shawky, N. (2020). The Development and Validation of Quality of Life Scale for Iraqi Patients with Type 2 Diabetes Mellitus. *Journal of Pharmacy & Bioallied Sciences*, *12*(3), 262–268. https://doi.org/10.4103/jpbs.JPBS_190_19

Monnier, L., Colette, C., Dunseath, G. J., & Owens, D. R. (2007). The Loss of Postprandial Glycemic Control Precedes Stepwise Deterioration of Fasting with Worsening Diabetes. *Diabetes Care*, *30*(2), 263–269. https://doi.org/10.2337/dc06-1612

Mostafa, N. M., Ahmed, G. H., & Anwar, W. (2018). Effect of Educational Nursing Program on Quality of Life for Patients with Type II Diabetes Mellitus at Assiut University Hospital. *J. Nurs. Educ. Pract*, *8*(11).

Najim, H. D., Majeed, I. A., & Rahmah, A. M. (2014). Effects of Metformin &/or Glimepiride on Resistin Level and Related Biochemical Markers in Type 2 Diabetes Mellitus. *Al Mustansiriyah Journal of Pharmaceutical Sciences*, *14*(2), 78–88.

Prajapati, V. B., Blake, R., Acharya, L. D., & Seshadri, S. (2018). Assessment of Quality of Life in Type II Diabetic Patients using the Modified Diabetes Quality of Life (MDQoL)-17 questionnaire. *Brazilian Journal of Pharmaceutical Sciences*, *53*.

Sazan, D. S., Kassim, J. S., & Ansam, N. H. (2012). Comparative Study between Metformin, Glibenclamide and their Combination in Newly Diagnosed Diabetic (type II) Patients in Hawler City. *Al Mustansiriyah Journal of Pharmaceutical Sciences*, *12*(2), 61–74.

Solomon, S. D., McMurray, J. J. V, Claggett, B., de Boer, R. A., DeMets, D., Hernandez, A. F., Inzucchi, S. E., Kosiborod, M. N., Lam, C. S. P., & Martinez, F. (2022). Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine*, *387*(12), 1089–1098.

Tamez-Pérez, H. E., Proskauer-Peña, S. L., Hernández-Coria, M. I., & Garber, A. J. (2013). AACE Comprehensive Diabetes Management Algorithm 2013. *Endocrine Practice*, *19*(4), 736.

Vanstone, M., Rewegan, A., Brundisini, F., Dejean, D., & Giacomini, M. (2015). Patient Perspectives on Quality of Life with Uncontrolled Type 1 Diabetes Mellitus: A Systematic Review and Qualitative Meta-synthesis. *Ontario Health Technology Assessment Series*, *15*(17), 1.

Verma, K., & Dadarwal, M. (2017). Diabetes and quality of life: A Theoretical Perspective. *Journal of Social Health and Diabetes*, *5*(01), 5–8.

Vijan, S., Sussman, J. B., Yudkin, J. S., & Hayward, R. A. (2014). Effect of Patients' Risks and Preferences on Health Gains With Plasma Glucose Level Lowering in Type 2 Diabetes Mellitus. *JAMA Internal Medicine*, *174*(8), 1227–1234. https://doi.org/10.1001/jamainternmed.2014.2894

Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Silverman, M. G., Zelniker, T. A., Kuder, J. F., & Murphy, S. A. (2019). Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*, *380*(4), 347–357.