https://doi.org/10.31351/vol33iss3pp142-149

Influence of Adding Empagliflozin to Conventional Anti-diabetic Therapy on Quality of Life Scale for Type 2 Diabetic Patients

Hadeel Delman Najim [*,1], Mohammed Mahmood Mohammed[2] and Abbas Mahdi Rahmah[3]

[1]Department of Clinical Pharmacy, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
[2]Department of Clinical Pharmacy, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
[3]National Diabetes Center for Treatment and Research, Mustansiriyah University, Baghdad, Iraq

[*]**Corresponding author**
Received 12/6/2023, Accepted 12/9/2023, Published 15/9/2024

Abstract

To evaluate the efficacy of empagliflozin on the quality of life (QoL) and glycemic index in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with conventional oral anti-diabetic agents (OADs).

A pre-post study involved forty T2DM patients who were on a combination of three OADs (glimepiride + metformin + vildagliptin) with glycated hemoglobin A1c (HbA1c) 7.0% - 12.0%. All patients received empagliflozin (10 mg/day) as add-on therapy for 16 weeks.

Adding empagliflozin showed significant reduction in postprandial plasma glucose (PPG), (HbA1c), body mass index (BMI) and index of central obesity (ICO) ($p<0.001$). Significant improvements have been shown in the Quality of Life in Iraqi type 2 diabetic patients (QOLSID) scores post-intervention ($p<0.001$). Besides, good QoL was reported in patients with lower BMI and among those who had DM for duration less than 10 years.

The outcome of this study showed that empagliflozin as add-on to oral antidiabetic triple therapy in poorly controlled T2DM has achieved a better weight management, well glycaemic control and enhanced QoL through the therapy, and was well tolerated among the study sample.

Keywords: Empagliflozin, Glycemic index, Quality of life, SGLT2 inhibitors, Type 2 DM.

تأثير إضافة إمباغليفلوزين إلى العلاج التقليدي المضاد لمرض السكري على مقياس جودة الحياة لمرضى السكري من النوع الثاني

هديل دلمان نجم*[،١]، محمد محمود محمد[٢]و عباس مهدي رحمة[٣]

[1]فرع الصيدلة السريرية، كلية الصيدلة، الجامعة المستنصرية ، بغداد ،العراق
[2]فرع الصيدلة السريرية، كلية الصيدلة ، الجامعة المستنصرية ، بغداد ،العراق
[3]المركز الوطني لعلاج السكري، الجامعة المستنصرية ، بغداد، العراق

الخلاصة:

تقييم فعالية إمباغليفلوزين على جودة الحياة (QoL) ومؤشرات نسبة السكر في الدم في المرضى الذين يعانون من مرض السكري من النوع الثاني غير المسيطر عليه بشكل كافٍ باستخدام الأدوية التقليدية لعلاج السكري عن طريق الفم .

الدراسة قائمة على متابعة أربعين مريضًا بالسكري من النوع الثاني يتناولون علاجا مكونا من ثلاثة ادوية فموية مضادة للسكري (جليمبيريد + ميتفورمين + فلداجليبتين) مع نسبة الهيموجلوبين السكري (HbA1c) ٧ % – ١٢ %حيث تلقى جميع المرضى دواء إمباغليفلوزين (١٠ ملغ / يوم) كعلاج إضافي لمدة ١٦ أسبوعًا.

أظهر إمباغليفلوزين انخفاضًا معنويًا في جلوكوز البلازما بعد الأكل و الهيموجلوبين السكري ومؤشر كتلة الجسم ومؤشر السمنة المركزية ($p<0.001$). تم الحصول على تغييرات معنوية في مقياس جودة حياة المريض بعد العلاج ($p<0.001$) وتم ملاحظة ضعف جودة حياة المريض في المرضى الذين يعانون من ارتفاع مؤشر كتلة الجسم والذين لديهم مرض السكر لمدة اكثر من ٥ سنوات.

أظهرت نتائج هذه الدراسة أن دواء إمباغليفلوزين كمكمل إضافي للعلاج الثلاثي في مرض السكري من النوع الثاني قد حقق فقدان الوزن وتحسين التحكم في نسبة السكر في الدم وتحسين نوعية الحياة.

الكلمات المفتاحية: إمباغليفلوزين، مؤشرات نسبة السكر، جودة حياة المريض، مثيطات نواقل الصوديوم والجلوكوز، السكر النوع الثاني.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease with a high prevalence rate [1]. The pharmacologic management of diabetes changes over time due to its progressive nature [2], this makes achieving optimal glycemic control with single therapy a challenge and finally most patients will need a combination of oral anti-diabetic agents (OADs), as reported by both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [3]. According to ADA, a combination therapy is needed when glycosylated hemoglobin (HbA1c) is ≥1.5% above the glycemic target and the add-on medication should have an impact on glycemic and weight management as well [3–6]).

Recent studies on T2DM therapies focused on the finding agents with multiple targets and minimum adverse effects, to control the possible complications of DM and improve the patient's life as a whole [7]. Of OADs, metformin still the first-line pharmacotherapy agent in T2DM for its insulin-sensitizing and weight-reduction effects [8,9]. The most recent OADs classes associated with weight control, cardiorenal benefits and a low risk of hypoglycemia are dipeptidyl peptidase-4 inhibitors (DPP4i); glucagon-like peptide-1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) [10–12]. Older oral antidiabetic group of medications such as thiazolidinediones (TZDs) and sulfonylureas (SUs) have good glycemic control but associated with multiple adverse effects such as hypoglycemia [13], edema, increased risk of heart failure [14], and weight gain [13,14].

Sodium glucose cotransporter 2 inhibitors (SGLT2i) is considered the newest class of OADs approved for the treatment of T2DM without associated-hypoglycemia and have favorable effects on body weight and cardiorenal outcomes. Empagliflozin; a selective SGLT2i currently available in Iraq; acts by blocking the renal glucose reabsorption through the SGLT2 transporter [15]. Clinical trials have been approved the safety and efficacy of empagliflozin mostly in cardio-renal outcomes in T2DM [16–18].

Patients' perspectives on how healthcare and medical interventions have affected their lives can now be assessed and taken into consideration in clinical decision-making, for this current orientation now toward the quality of life (QoL) measures [19]. A number of questionnaires have been developed by the WHO to measure QoL [20] and by EuroQol Group [21] and other institutes. Multiple studies have been found a correlation between QoL and many factors such as gender, duration of DM, occupation, and the occurrence of complications [22,23].

Quality of Life Scale for Iraqi DM patients (QOLSID) was designed to assess quality of life among Iraqi T2DM patients. Development and validation of this tool were done by Ehab et al., and approval was taken directly from the author to use this questionnaire [24]. Thus, to determine the effectiveness of new treatment for DM patients, assessing the improvement in both glycemic control and the patient QoL is considered an important measure of outcomes [25–27].

The class of SGLT2i has several adverse effects, including hypotension, ketoacidosis, acute kidney injury, genital mycotic infections and urinary tract infections, hypoglycemia (when used in combination with insulin secretagogues or insulin injections) [28,29].

This study was designed to determine the impact of a SGLT2i; empagliflozin; as add-on therapy on glycemic status and QoL in a sample of Iraqi T2DM patients already treated with oral antidibetic agents (OADs) in Baghdad.

Methods

Study Design

This pre-post study that was conducted from May to December 2022, at the National Diabetic Centre for treatment and research/ Mustansiriyah University/ Iraq. The ethical committee of the diabetes center and the college of pharmacy in Mustansiriyah University gave their approval before the study initiation. All patients were fully informed about the study protocol and written consent was obtained from all participants before starting the study. All investigations and procedures carried out in this study involving human participants were in accordance with the 1975 Declaration of Helsinki and its later amendments.

Participants Recruitment

Fourty four patients were enrolled in the study with the following criteria: T2DM, age between 18-70 years, on a combination of OADs (glimepiride + metformin + vildagliptin), with HbA1c (7% - 12%) at the time of enrollment. Patients who met the inclusion criteria and agreed to the study protocol were recruited; a written consent was obtained from all participants before starting the study. All patients were received empagliflozin 10mg (Getz, Pakistan) once daily for 16 weeks. Glimepiride was down-titrated during the treatment period to mitigate the risk of recurrent hypoglycemic events at the discretion of the investigator. All the mentioned steps were done under the supervision of specialist physician.

Outcome Measures

The study's outcomes measured the changes before and after treatment with empagliflozin (at week 0 and 16). The following parameters were measured: QoL, HbA1c, postprandial plasma glucose (PPG; glucose level measured 2 hours after standardized breakfast). Serum glucose level was measured using enzymatic method with hexokinase [30] on the cobas c311 analyzer system (Roche,

Hitachi/Germany), while HbA1c level was measured using the Tina-quant Hemoglobin A1c Dx Gen.3 assay [31] on the cobas c503 analyzer (Roche, Hitachi /Germany). Body weight (BW) and height (Ht) were measured using the Height/weight scale (Kinlee/China). Body mass index (BMI) was measured using the formula: [BMI=Weight(kg)/Height(m^2)] and classified according to the world health organization (WHO) [32]. Waist circumference (WC) was measured using a stretch-resistant tape at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest, the WC cut-off in men >94 cm and >80 cm in women [33]. Index of central obesity (ICO) was measured using the formula [ICO=WC(cm)/Height(cm)] and the ICO cutoffs ranged from 0.51 to 0.58 among males and 0.47 to 0.54 among females [34].

Quality of Life Assessment Tool

The QOLSID tool; introduced in 2020 by Ehab et al. [24]; was used in this study to measure the QoL in diabetic patients. The QOLSID questionnaire consists of 10 questions with five likert scale answers ranging from (0-4), questions 6,7 were with reversed order. Scores more than 32.5 indicates a good QoL. All selected patients were answered the questions by themselves and the questionnaire was presented to patients with unsatisfactory educational levels and those with visual impairment via a face-to-face interview with the researcher. Arabic version of the QOLSID was administered to the participants at baseline and after 16 weeks. The participants were interviewed in Arabic and their sociodemographic data were collected as well.

Statistical Analysis

Statistical analysis was performed using SPSS (version 29) and Microsoft excel (2010). Paired samples T-test was performed for comparison between before and after treatment values. Independent T-test was performed for comparison between patients' groups. A p-value of <0.05 was considered significantly different.

Results

The majority of involved patients completed the study (90.9%), with the commonest reasons for discontinuation being non-adherent with the study medication (2 cases), non-compliance with the appointment (2 cases). A total of 40 patients were completed the study, Table 1.

Glycemic index; PPG and HbA_{1c} levels; were significantly reduced after treatment with empagliflozin over 16 weeks ($p<0.01$). Moreover, BMI, WC and ICO were significantly reduced after treatment ($p<0.05$), Table 2. One case of mild urinary tract infection was recorded without affecting treatment plan.

Table 1. Patients' demographic and baseline characteristics

Demographic Characters			No (%)
Age (years)	≤60		32 (80)
	>60		8 (20)
Gender	Male		19 (47.5)
	Female		21 (52.5)
BMI (kg/m^2)	25 - 29.9		6 (15)
	30 - 34.9		15 (37.5)
	≥ 35		19 (47.5)
Waist Circumference (cm)	Male	≥ 94	19 (47.5)
	Female	≥ 80	21 (52.5)
Smoking	Yes		5 (12.5)
	No		35 (87.5)
Alcohol	Yes		0
	No		40 (100)
Educational level	Illiterate		11 (27.5)
	Primary		4 (10)
	Secondary		20 (50)
	College		5 (12.5)
Residence	Urban		29 (72.5)
	Rural		11 (27.5)
Monthly Income ($)	<500		20 (50)
	500-1000		20 (50)
Duration of DM (years)	<5		7 (17.5)
	5-10		7 (17.5)
	≥10		26 (65)

Continued Table1.

Family History of DM	Yes	30 (75)
	No	10 (25)
Medical history	Non	14 (35)
	Comorbid disease	26 (62.5)

Data presented as number and percentage, No (%).

Table 2. Laboratory values change from weeks 0 and week 16

Variables	Pre-treatment	Post-treatment	P-Value [a]
PPG (mg/dl)	287.85 ± 80.13	189.36 ± 49.90	< 0.001**
HbA1c (%)	9.03 ± 1.29	7.85 ± 0.74	< 0.001**
BMI (kg/m^2)	42.64 ± 34.24	41.51 ± 35.09	<0.001**
WC (cm)	112.69 ± 9.26	111.62 ± 9.14	0.001**
ICO	0.74 ± 0.20	0.73 ± 0.21	0.005**

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

Quality of Life Scale for Iraqi DM patients (QOLSID)

All questions of QOLSID have been answered at baseline and after 16 weeks of treatment with empagliflozin, a high significant change (p<0.001) was reported in the QOLSID score post treatment, shown in table (3). In most patients, empagliflozin showed a highly significant improvement in the satisfaction of the patients about the diet restriction, ability to do exercise, night sleep and the stress due to daily blood glucose testing. In addition, most patients were significantly satisfied about empagliflozin results and its ability to control diabetes (p<0.001). In the majority of the patients, empagliflozin significantly reduced stress and anxious towards diabetes (p<0.05). Most patients were more satisfied regarding their overall health after addition of empagliflozin to their medications (p<0.001).

Furthermore, the association of QoL with some demographic and disease characteristics, showed that patients with age (>60 years), having BMI<30, and having DM for duration 5-10 years were with higher QoL score than other groups (Good QoL >32.5) but with non-significant values (p≥0.05), Table 4.

Table 3. Effect of Empagliflozin on Quality of life (QOLSID) score after 16 weeks.

Questions	Pre-treatment	Post-treatment	p-value[a]
Q1 Satisfied with diet restriction required to control your diabetes?	2.67 ± 1.31	3.42 ± 0.83	0.005**
Q2 Satisfied with your current diabetes treatment?	2.54 ± 1.22	3.46 ± 0.72	<0.001**
Q3 Satisfied with your ability to do an exercise (e.g. brisk walking, cycling or swimming)?	1.25 ± 1.22	2.67 ± 0.92	<0.001**
Q4 Satisfied with your ability to control diabetes?	1.33 ± 1.37	2.67 ± 1.02	<0.001**
Q5 Satisfied with health care services that you receive?	3.64 ± 0.67	3.53 ± 0.68	0.423
Q6 Feeling stressed by blood glucose testing?	2.08 ± 1.47	3.17 ± 0.71	0.004**
Q7 Feeling stressed or anxious to diabetes?	3.21 ± 1.10	3.75 ± 0.44	0.029*
Q8 Satisfied with the support you get from your friends and family?	3.88 ± 0.34	3.96 ± 0.20	0.328
Q9 Satisfied with your night sleep?	1.79 ± 1.32	2.83 ± 0.64	<0.001**
Q10 Satisfied with your overall health?	1.67 ± 1.63	2.71 ± 1.49	0.002**
Total score	**23.42 ± 5.71**	**31.42 ± 4.42**	**<0.001****

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 4. Association of QOLSID with demographic and disease characteristics after treatment with Empagliflozin, n=40

Demographic and disease characters		QOLSID	p-value
Age (years)	≤ 60	30.48 ± 4.54	**0.29** **NS**
	> 60	32.37 ± 4.03	
Gender	Male	30.47 ± 4.68	**0.59** **NS**
	Female	31.25 ± 4.32	
BMI	25 - 29.9	33.67 ± 5.20	**0.44** **NS**
	30 - 34.9	29.75 ± 3.85	
	35 - 39.9	31.86 ± 4.22	
	≥ 40	31.67 ± 5.95	
Waist Circumference	Male ≥ 94	30.47 ± 4.68	**0.55** **NS**
	Female ≥ 80	31.33 ± 4.23	
Educational Level	Illiterate	31.09 ± 3.64	**0.84** **NS**
	Primary	31.00 ± 4.08	
	Secondary	31.25 ± 4.50	
	College	29.20 ± 6.60	
Family history	Yes	30.66 ± 4.65	**0.61** **NS**
	No	31.50 ± 4.03	
Monthly Income	<500	31.11 ± 4.47	**0.75** **NS**
	500-1000	30.65 ± 4.55	
Duration of DM (years)	<5	31.14 ± 4.49	**0.36** **NS**
	5-10	33.00 ± 4.62	
	≥10	30.30 ± 4.40	

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

Discussion

Diabetes mellitus is a chronic disease that has a negative impact on patients' physical, social and mental state. In addition, persistent hyperglycemia despite taking multiple OADs adds an extra burden on patient's life [23,35]. A report from the emotional and psychological support working group of NHS Diabetes and Diabetes UK stated that depression and anxiety significantly higher among diabetes patients due to raising concerns about the disease progression [36–38]. This is the first study on Iraqi T2DM patients to assess the QoL upon adding empagliflozin 10 mg once daily as add-on therapy with glimepiride, metformin, and vidagliptin. The QoL outcomes prior to empagliflozin add-on were compared with those obtained after 16 weeks of treatment. A significant improvement in the glycemic index mostly affected positively on other aspects related to QoL, this may be reflected on the morale and psychological condition of the patients as glucose control reduced their stress and anxiety.

Our findings are compatible with a previous study on T2DM patients with hypertension, assessed the QoL upon adding empagliflozin to triple antidiabetic therapy (metformin + teneligliptin + glimepiride) for 12 weeks. They confirmed QoL improvement due to Empagliflozin addition is proportional to the improvement in glycemic index which could reflect on other aspects of QoL like physical health, physical endurance, emotional/mental health, and diet satisfaction [39].

The same study reveald that better QoL was clear in normal weight individuals while long DM duration was related to worsen QoL consistent with the present study findings. Patients with poor glycemic control and long DM duration (>10 years) as well as higher BMI (≥30) were showed poor QoL, this could be related to the persistent glucose elevation due to insulin resistant or even lack of insulin reserve [40]. These results can partially explain the failure of the conventional therapy and emphasize the needs for an agents work by different mechanisms.

Regarding the glycemic status, adding empagliflozin significantly reduced HbA1c, PPG and weight indices, these results are consistent with the previous study by Eu Jeong Ku et al. which demonstrated the effectiveness of empagliflozin-based quadruple therapy with metformin, glimepiride and DPP4i in comparison with insulin-based therapy in patients with inadequately controlled T2DM during 24 weeks [41]. These results were in accordance with other studies evaluated the effectiveness of empagliflozin as add-on therapy with metformin and other OADs regarding glycemic and weight management [42–44]. Increasing evidence suggests that the postprandial hyperglycemia is a contributing factor to the development of long-term complications in T2DM [45,46], and it is the major determinant of HbA1c level. Thus, correcting postprandial hyperglycemia may form part of the strategy for the controlling and preventing the disease complications [47].

The reduction in body weight is a notable feature of SGLT2i, make them useful agents to combine with other OADs for both glycemic control and weigh loss [48–50]. In present study, adding empagliflozin significantly reduced body weight and waist circumference which confirms its role in mitigating weight gain effect of other diabetic medications. The main contributor to this effect is caloric loss due to increase urinary glucose excretion by empagliflozin [51,52]. Empagliflozin was well tolerated in Iraqi patients during the treatment time, except for three patients reported mild urinary tract infection.

The study had the following limitations. The small sample size, as this is the first study on empagliflozin 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

In conclusion, the results of this study showed that adding empagliflozin pill to the triple therapy in poorly controlled T2DM has helped in achieving weight reduction, better glycaemic control and quality of life in addition to being well tolerated in the study sample. Larger sample size and longer-term studies in different countries are necessary to confirm the efficacy and tolerability of empagliflozin on other population.

Acknowledgment

The authors of this research would like to thank College of Pharmacy/ Mustansiriyah University in Baghdad-Iraq for their continued support in order to complete this study and for their help in providing the practical platform of this study.

Conflicts of Interest

There is no conflict of interest.

Funding

The research was not funded by any institution.

Ethics Statements

The ethical committee of the Diabetes Center and of the College of Pharmacy in Mustansiriyah University gave their approval before the study initiation.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Hadeel Delman Najim, Mohammed Mahmood Mohammed, Abbas Mahdi Rahmah; data collection: Hadeel Delman Najim, Abbas Mahdi Rahmah; analysis and interpretation of results: Hadeel Delman Najim, Mohammed Mahmood Mohammed, Abbas Mahdi Rahmah; draft manuscript preparation: Hadeel Delman Najim, Mohammed Mahmood Mohammed. All authors reviewed the results and approved the final version of the manuscript.

References

1. IDF. International Diabetes Federation. IDF Diabetes Atlas . http:// www. idf. org /diabetesatlas. Vol. 6th editio, Brussels, Belgium: International Diabetes Federation. 2013.
2. Associaton AD. Diagnosis and classification of diabetes mellitus. Vol. 37, Diabetes care. Am Diabetes Assoc; 2014.
3. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. 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. 2012;55(6):1577–96.
4. Association AD. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S98–110.
5. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. 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. 2022 Sep 28;45(11):2753–86.
6. Hadi RA, Mohammed MM, Salman IN. Studying the Effect of Adding Alpha Lipoic Acid to Gabapentin to Improve Nerve Conduction Velocity and Glycemic Control of Patients with Diabetic Neuropathy (Sample of Iraqi population). Al-Mustansiriyah J Pharm Sci. 2020;20(1).
7. Li Y-Y, Yang Y-M, Zhu S, Cheng H, Hernandez J, Huang W, et al. Changes in body weight and cardiovascular risk factors in a Chinese population with type 2 diabetes mellitus: a longitudinal study. Front Endocrinol (Lausanne). 2023;14:1112855.
8. Najim HD, Majeed IA, Rahmah AM. Effects of Metformin &/or Glimepiride on Resistin Level and Related Biochemical Markers in Type 2 Diabetes Mellitus. Al Mustansiriyah J Pharm Sci. 2014;14(2):78–88.
9. Yerevanian A, Soukas AA. Metformin: Mechanisms in Human Obesity and Weight Loss. Curr Obes Rep. 2019;8(2):156–64.
10. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, et al. 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, Obes Metab. 2014;16(2):159–69.

11. Rowlands J, Heng J, Newsholme P, Carlessi R. Pleiotropic Effects of GLP-1 and Analogs on Cell Signaling, Metabolism, and Function. Front Endocrinol (Lausanne). 2018;9:672.

12. Thrasher J. Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies. Am J Med. 2017 Jun;130(6S):S4–17.

13. Galindo RJ, Dhatariya K, Gomez-Peralta F, Umpierrez GE. Safety and Efficacy of Inpatient Diabetes Management with Non-insulin Agents: an Overview of International Practices. Curr Diab Rep. 2022 Jun;22(6):237–46.

14. Nesti L, Tricò D, Mengozzi A, Natali A. Rethinking pioglitazone as a cardioprotective agent: a new perspective on an overlooked drug. Cardiovasc Diabetol. 2021;20(1):109.

15. Association AD. Economic costs of diabetes in the US in 2012. Diabetes Care. 2013;36(4):1033–46.

16. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023 Jan;388(2):117–27.

17. Moher D, Hopewell S, Schulz KF. Empagliflozin and progression of kidney disease in type 2 diabetes. New Engl J Med. 2008;358:2560–72.

18. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24.

19. Addington-Hall J, Kalra L. Who should measure quality of life? BMJ. 2001 Jun;322(7299):1417–20.

20. Gholami A, Jahromi LM, Zarei E, Dehghan A. Application of WHOQOL-BREF in measuring quality of life in health-care staff. Int J Prev Med. 2013;4(7):809.

21. Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. Appl Health Econ Health Policy. 2017;15:127–37.

22. Abedini MR, Bijari B, Miri Z, Shakhs Emampour F, Abbasi A. The quality of life of the patients with diabetes type 2 using EQ-5D-5 L in Birjand. Health Qual Life Outcomes. 2020;18(1):1–9.

23. Prajapati VB, Blake R, Acharya LD, Seshadri S. Assessment of quality of life in type II diabetic patients using the modified diabetes quality of life (MDQoL)-17 questionnaire. Brazilian J Pharm Sci. 2018;53.

24. Mikhael EM, Hassali MA, Hussain SA, Shawky N. The Development and Validation of Quality of Life Scale for Iraqi Patients with Type 2 Diabetes Mellitus. J Pharm Bioallied Sci. 2020;12(3):262–8.

25. Ishii H, Niiya T, Ono Y, Inaba N, Jinnouchi H, Watada H. 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. Diabetol Metab Syndr. 2017;9:3.

26. Aso Y, Suzuki K, Chiba Y, Sato M, Fujita N, Takada Y, et al. 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 Res Clin Pract. 2017 Aug;130:237–43.

27. Mostafa NM, Ahmed GH, Anwar W. Effect of educational nursing program on quality of life for patients with type II diabetes mellitus at Assiut University Hospital. J Nurs Educ Pr. 2018;8(11).

28. Administration USF and D, Commission FDADS. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Accessed 21 July 2021.

29. Douros A, Lix LM, Fralick M, Dell'Aniello S, Shah BR, Ronksley PE, et al. Sodium–glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: a multicenter cohort study. Ann Intern Med. 2020;173(6):417–25.

30. White CA, Kennedy JF. Methods of enzymatic analysis, volume VI: Metabolites 1: Carbohydrates edited by HU Bergmeyer, J. Bergmeyer and M. GraRl, Verlag Chemie, Weinheim, 1984. pp. xxix+ 701, individual volume price 150.00,DM350.00;seriessubscriptionprice 130.00, DM 295.00. ISBN. Wiley Online Library; 1985.

31. Goldstein DE, Little RR, Wiedmeyer HM, England JD, McKenzie EM. Glycated hemoglobin: methodologies and clinical applications. Clin Chem. 1986 Oct;32(10 Suppl):B64-70.

32. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Vol. 894, World Health Organization technical report series. Switzerland; 2000.

33. Organization WH. Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008. 2011;

34. Parikh RM, Joshi SR, Menon PS, Shah NS. Index of central obesity - A novel parameter. Med Hypotheses. 2007;68(6):1272–5.

35. Kalra S, Jena BN, Yeravdekar R. Emotional and psychological needs of people with diabetes. Indian J Endocrinol Metab. 2018;22(5):696.

36. Diabetes NHS. Emotional and psychological support and care in diabetes. Rep from Emot Psychol Support Work Gr NHS Diabetes

Diabetes UK. 2010;
37. Lai TC, McDaniel CC, Chou C. Diabetes management behaviors associated with depression in the U.S. Diabetol Metab Syndr. 2022 Nov;14(1):178.
38. Akhaury K, Chaware S. Relation Between Diabetes and Psychiatric Disorders. Cureus. 2022 Oct;14(10):e30733.
39. Najar IA, Masoodi SR, Mir SA, Bhat MH, Patyar RR, Patyar S. Impact of empagliflozin add-on therapy on quality of life in patients of type 2 diabetes mellitus with hypertension: A prospective study. Indian J Public Health. 2022 Nov;66(Supplement):S41–4.
40. Salman IN. β-Cell function in a sample of Iraqi Patients with type 2 diabetes mellitus Isam Noori Salman. Al Mustansiriyah J Pharm Sci. 2018;18(1):68–72.
41. Ku EJ, Lee D-H, Jeon HJ, Oh TK. Effectiveness and safety of empagliflozin-based quadruple therapy compared with insulin glargine-based therapy in patients with inadequately controlled type 2 diabetes: An observational study in clinical practice. Diabetes Obes Metab. 2019 Jan;21(1):173–7.
42. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes, Obes Metab. 2014;16(2):147–58.
43. Neeland IJ, McGuire DK, Chilton R, Crowe S, Lund SS, Woerle HJ, et al. Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus. Diabetes Vasc Dis Res. 2016 Mar;13(2):119–26.
44. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes, Obes Metab. 2013;15(12):1154–60.
45. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care. 2007 Feb;30(2):263–9.
46. Faruqui A. Post Prandial Hyperglycemia: A Real Threat for Patients with Type 2 Diabetes Mellitus. 2017;
47. Ceriello A. Postprandial Hyperglycemia and Diabetes Complications: Is It Time to Treat? Diabetes. 2005 Jan 1;54(1):1–7.
48. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes Obes Metab. 2013 Aug;15(8):721–8.
49. Devineni D, Morrow L, Hompesch M, Skee D, Vandebosch A, Murphy J, et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes Obes Metab. 2012 Jun;14(6):539–45.
50. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. 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. J Clin Endocrinol Metab. 2012 Mar 1;97(3):1020–31.
51. Perry RJ, Shulman GI. Sodium-glucose cotransporter-2 inhibitors: Understanding the mechanisms for therapeutic promise and persisting risks. J Biol Chem. 2020 Oct;295(42):14379–90.
52. Fishman B, Shlomai G, Twig G, Derazne E, Tenenbaum A, Fisman EZ, et al. Renal glucosuria is associated with lower body weight and lower rates of elevated systolic blood pressure: results of a nationwide cross-sectional study of 2.5 million adolescents. Cardiovasc Diabetol. 2019;18(1):124.