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SGLT2 inhibitor: metabolic effect on Libyan patients with T2DM at National Diabetes Center in Tripoli

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Abstract:T2DM is a progressive disease with a complex pathophysiology.The kidney plays an important role in glucose homeostasis, partly via the reabsorption of glucose from the glomerular filtrate. Empagliflozinis an effective and highly selectivesodium glucose cotransporter-2 inhibitor ((SGLT2).This study aimedto assess metabolic effect of empagluazin in Libyan patients withuncontrolled T2DM at National Diabetes Center, Tripoli, Libya in 2019.Prospective interventional study, lasting for 24 weeks, included patients with uncontrolled T2DM, given EMPA as an add on oral, once daily, anti-hyperglycemic treatment for patients with inclusion criteria: age ≥18 years, high risk for cardiovascular diseases, patient with established CVD and patient with satisfactory renal function e-GFR > 30 ml/min. Efficacy endpoints are change in HbA1c, bodyweight,Bp, S. Na, fasting LDL-Cfrom baseline at 4 week, 12 weeks and at 24 weeks.Data analysis was done by SPSS program version 16.A total of 40 patients included in the study, female were 70%, mean age was 62.05±9.77, (67.5%)were obese,mean body weight was 89.32±21.75, 67.5% were more than 10 years duration of T2DM, 67.5% were known hypertensive, 72.5% were known CVD. There mean S. Na level were 140± 4.78, their HBA1c were 10.3±1.83, 57.5% with previous history of urinary tract infection, starting Empagliflzin, following with body weight,Bp, urine routine,S Cr,S.Naevery 2-week,4-week,12-week and 24-week and HBA1c, fasting lipid at 12 and 24 week showna reduction in HBA1c by -3.72 to -2.64.Reduction in body weight,especially in initial 4-week and obese casesby-14.4 to -9.78 kg, systolic Bpshows drop especially in hypertensive cases (-10.05 to-4.08) with high S Na at presentation (-4.56 to 1.8),initial mild train set increase in S Cr (0.03to0.19) followed by reduction with moderate improvement in e-GFR (within same stage in CKD),no significant changes in fasting lipid profile may be due to continue intake of statin. In

conclusion,Empagliflzin is a potent, anti-hyperglycemic drug with a good metabolic effect showed reductions in glycated hemoglobin, marked reductions in the body weight and systolic Bp, thus, supporting the use of empagliflozin as a mono-therapy or in addition to other glucose-lowering agents especially in patients with T2DM and increased cardiovascular risk.

Keywords: Type 2 diabetes mellitus, sodium glucose co-transporter-2 inhibitor,Empagliflozin,cardiovascular disease, chronic kidney disease, Libya

Introduction

Type II diabetes mellitus (2DM) is a progressive disease with a complex pathophysiology (1).Increasing insulin resistance, progressive deterioration of β-cell function, dysfunctional adipocytes, gastrointestinal incretin defects, and increased glucose reabsorption from the kidneys, hyper-glucagonemia and neurotransmitter dysfunction may contribute to development of diabetes (1).The kidney plays an important role in glucose homeostasis, active glucose reabsorption in the kidney is mediated by two sodium glucose cotransporter (SGLT) proteins, SGLT1 and SGLT2 (2).Empagliflozin (Jardiance®), an effective, highly selective, (SGLT2) inhibitor, gives the suitability of once-daily oral administration and carries a low risk of hypoglycemia as a result of its insulin-independent mode of action, allowing it to be used as monotherapy or as add-on therapy to other anti-diabetic agents with complementary modes of action and generally well tolerated. Beyond glycemic control,empagliflozinemploysanadvantageou s effect including modest decrease in bodyweight and blood pressure ,as well as it established cardio-renal protective properties in patients with T2D and recognized cardiovascular disease (CVD) ; as reductıon ın systolıc blood pressure, serum sodium, that may lead to reduction in pre-load on heart. Inhibition of SGLT2-mediated glucose transport in the kidney decreases the threshold at which urinary glucose excretion happens, which results in loss of glucose in the urine and a reduction in hyperglycemia. SGLT2 inhibition has been reported to reduce the renal threshold to approximately 3.3 mmol/L (60 mg/dl) in healthy individuals and to approximately 3.9 - 5.0mmol/l (70 - 90 mg/dl) in individuals with T2DM .Thatwas the basis for the use of SGLT2 inhibitors for glucose-lowering therapy in T2DM. Also, as SGLT2 inhibitors have a unique mechanism of action that does

not depend on a functioning pancreatic β-cell, they have several potential advantages over other classes of glucose-lowering agents in the treatment of T2DM .They should theoretically be effective in patients with any degree of β-cell function (i.e., in early vs advanced disease duration), should not confer a further risk of hypoglycemia (unless combined with insulin or an insulin secretagogue) and have the possible to provide additional glucose lowering when combined with other classes of antihyperglycemic agents. In addition, the associatedurinary glucose excretion results in loss of calories (possibly producing, weight reduction) and the osmotic diuretic effect may reduce blood pressure.

On top of standard of care, empagliflozin demonstrated cardiovascular benefits, a 14% reduction in risk of the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, which can benefit patients with T2DM and at high risk of cardiovascular disease.The ADA/European Association for the Study of Diabetes (EASD) updated position statement recommends that SGLT2 inhibitors be used at any stage of T2DM owing to their insulin-independent mechanism of action [1]. They are positioned as a "reasonable second-line or third-line" option as add-on to other glucose-lowering therapy. The AACE/American College of Endocrinology (ACE) and ADA Standards of Medical Care in Diabetes guidelines recommend SGLT2 inhibitors as an initial therapeutic option when metformin is contraindicated.SGLT2 inhibitors are also recommended as a component of dual and triple therapy.

In this study,empagliflozin has also been assessed in special subpopulations with T2DM, including patients with high risk of cardiovascular disease; chronic kidney disease (CKD),hypertension, obesity, as well as in elderly patients.The study also addressed concerns of possible train setdeterioration in renal function due to treatment with SGLT2 inhibitors as well as the improvement in Urine albumin to creatinine ratios with empagliflozincompared with before treatment (1).Thus, the metabolic effect ofempagliflozin in Libyan patients with uncontrolled T2DM at National Diabetes Center, from April to October 2019, for glycemic control, effect in body weight, systolic Bp, S sodium, S creatinine .as well as HBA1c, fasting LDL-cholesterol, uric acid,e-GFR was evaluated.

Materials and Methods

Prospective interventional study included 40 patients, with uncontrolled T2DM, given EMPA as add on oral once dailyanti- hyper glycemic treatment for patients with inclusion criteria:welling to anticipate in the Exclusion criteria:any problem in urinary tract that could result in urine stasis and recurrent urine tract infection (as male with history of prostatic hypertrophy), cases with low serum sodium (130mg/dl), moderate to severe hepatic impairment, Impaired renal function, defined as Glomerular Filtration Rate <30 ml/min, planned cardiac surgery or angioplasty within three months, acute coronary syndrome, stroke or TIA within 2 months prior to informed consent, current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM.Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption, blood-dyscrasias, medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer study, adult Age ≥ 18 years,high risk for CVD or patient with established CVDand patient with satisfactory renal function eGFR> 30 ml/min, after application of exclusion criteria.

within the last 5 years, treatment with anti-obesity drugs (e.g. sibutramine, orlistat) 3 months prior to informed consent or any other treatment at the time of screening leading to unstable body weight, pre-menopausal women who are nursing or pregnant or and are not practicing an acceptable method of birth control (1).A special Performa was completed for every patientwith inclusion criteria, after verbal consent taken for frequent monitoring andregular follow up during study period 24 week (April till October 2019 p).Follow up with life style education, body weightand blood pressure measures, also urine routine test , S Cr, S. Na analysis every 2-week, 4 week,12-week and 24-week as well as HBA1c,fasting lipid at 12 and 24-week, adjustment in diuretic dose and anti-hypertensive drugs as well as anti-hyperglycemic drugs mostly insulin doses.

Follow up sheet

Character	baseline	2-wk	4 -wk	12 -wk	24 -wk	Sig (2-tailed)
HBA1C	10.30±1.83	♯	♯	8.35±0.8	7.12±0.4	0.000 -3.72 to -2.64
Body Weight	89.32±21.75	♯	85.35±20.73	81.02±18.66	77.22±16.9	0.000 -14.41 to-9.78
Systolic BP	1.35±13.95	1.35±13.95	1.30±9.25	1.29±8.08	1.28±7.59	0.000 -10.05 to-4.08
s. Na	140±4.59	138.9 ±2.6	137.8±2.20	137±1.81	137±1.66	- 4.56 to 1.8
S Uric acid	6.42±1.3	♯	♯	♯	5.95±1.08	0.000 1.69 to 1.31
Albumin in urine	55.25±104.72	♯	♯	♯	19.02±7.76	0.000 1.81 to 1.19
e GFR	1.23±85.5	♯	♯	♯		
S. Cr	0.83±0.25	♯	♯	♯	0.94±0.13	0.007 0.03to0.19
H/o UTI	No 23(57.5%) after treatment 17(42.5%)	Need treatment 20 (50%)	Need treatment 23(57.5%)	Need treatment 19(47.5%)	no 23(57.5%)	Same as pre-treatment

Statistical analysis:Thiswas performed by using the statistical package for social science program (SPSS) version “16”. Non parametric test with K related sample (Friedman test) was used.

Results and discussion

It was aimed in the present study to asses metabolic effect of empagliflozinin Libyan patients with uncontrolled T2DM at National Diabetes Center during 24-week for glycemic control, effect in body weight, systolic Bp, S sodium, S creatinine. Fasting lipid, uric acid,e-GFR. We include 40 patientswith T2DM, 11 cases (27.5%)high risk for CVD and 29 cases (72.5%) with established CVD,uncontrolled hyperglycemia (all cases with HBA1c above 8.0 g%) with preserved renal function (e-GFR>30 ml/hr), their S Na were above 130 mg/dl, urine R/E were free of urinary tract infection.Majority of our studied group were above 40 years of age with mean (62.05 ± 9.77) and 28 (70%) were female, with long duration of T2DM(27 cases with more than 10 year diagnosis with T2DM) thatreflectedhigherprevalence of CVD in old, women with prolonged duration of DM than male. Mostof our patients were over-weight and obese (about 35 cases,90%) their body weight above target, that more than two third (27, 67.5%)were obese with (BMI >30 kg/m^2). Weight reduction was significant in this group (patient with 168 kg body weight lost 14 kg within 6 months)with diet management and encourage exercise without any other pharmacological treatment for obesity.Over-all there was significant reduction in weightwithin 6 month (-14.41 to-9.78)thatattributed to life style modification as well as to reduction in insulin resistance and improve of glycemic control with lowest insulin dose required that was higher than the figures shown in well-

Table 1: Socio- demographic and clinical characteristics of patients at National Diabetes Center.

Characters	No. (%)
Age in years62.05±9.77 18-40 41-63 ≥64	Range 33 - 83 years 01 (2.5%) 20 (50%) 19 (47.5%)
Sex Female	 28 (70%

male	12 (30 %)
Body Mass Index89.32±21.75	Rang 57-168kg
Normal	4(10%)
Over weight	9 (22.5%)
Obese	27(67.5%)
Duration of DM	
<1year	1(2.5%)
2-9 years	12 (30%)
>10 years	27 (67.5%)
Treatment of DM	
Oral hypoglycaemic drugs	10(25%)
Insulin	7 (17.5%)
Combined	23(57.5%)
Presence of hypertension	
Yes	27(67.5%
No	13(32.5%)
Cardio-vascular disease	
Yes	29(72.5%)
No	11(27.5%)

known previous study use of empagliflozin as monotherapy or add on to metformin, or as add-on to metformin plus sulfonylurea, consistently resulted in significant reductions in body weight from baseline, at 24 weeks ranging from 2.1-2.5 kg ($p< 0.001$) (3-7).But when add to pioglitazone (with or without metformin) or insulin, reductions in body weight were smallranging from 0.9 - 1.7 kg(8,9).In a 52-week phase 3 study of empagliflozin as add-on to multiple daily injections of insulin in obese individuals (body mass index ≥30 and ≤45 kg/m^2), empagliflozin was shown to improve glycemic control, reduce insulin dosage requirements, and decrease body weight compared with placebo 10Significant reductions in HbA1c from baseline were also seen at week 52 with both empagliflozin 10 mg and 25 mg (both $p<0.001$ vs placebo).The study show significant improvement in glycemic control with steady reduction in HBA1C (-3.72 to -2.64 with $P < 0.001$),the starting HBA1c were

high (10.30± 1.83),after 12 weeks were reduced (8.35± 0.8), than at the end of study there was further improvement (7.12±0.4), no risk of hypo-glycemiawere observed in our studied sampleThat was supported with previous studies whenempagliflozin add on other anti-hyperglycemic agent ,such as metformin in (EMPA-REG MET) (3) 24-week study, shown reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo ($p<0.001$. Additionally, a 52-week extension study (EMPA-REG EXTEND MET) also showed sustained reductions in HbA1c (7). Adjusted mean reductions in FPG at 76 weeks were significantly greater with both doses of empagliflozin compared with placebo (both $p< 0.001$). Also, in a 24-week, placebo-controlled, phase 3 study of empagliflozin with sitagliptin reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo ($p<0.0001$), but not greater compared with sitagliptin ($p=0.970$. In patients with HbA1c ≥8.5% at baseline, empagliflozinwas associated with significantly greater reductions in HbA1c at week 24 than with sitagliptin. At week 24, adjusted mean changes from baseline in FPG were greater with empagliflozin than with placebo or sitagliptin ($p<0.001$) (6). These improvements in glycemic control were sustained over a 52-week extension study (EMPA-REG EXTEND MONO) (12).As well as in 24-week phase 3 study comparing empagliflozin 10 mg and 25 mg with placebo as add-on to metformin plus sulfonylurea (EMPA-REG MET SU) (4), reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo ($p<0.001$). Additionally a study (EMPA-REG BASAL) were randomized patients with inadequate glycemic control (HbA1c >7.0% - 10.0%) despite treatment with stable basal insulin, with or without concomitant metformin and/or sulfonylurea to receive add-on therapy with once-daily empagliflozin 10 mg, 25 mg or placebo (9).The decrease in HbA1c levels from baseline to week 18 (primary endpoint) was significantly greater with both doses of empagliflozin than with placebo (both $p<0.001$). Presence of hypertension were the most associated risk for CVD in our studied sample (27 cases 67.5%), the study show gradual improvementin systolic B p records(-10.05 to- 4.08) that observed within first week of initiation of empagliflozin,with no hypotension attack,that could be explained with remove of extra sodium that well recorded in patient with higher sodium levels.S Na levels were (140 ± 4.59) ,that was high especially in cases with higher

systolic Bp,after 6week of study there were reduction of S Na in this group (137±1.66) that reflected with good control of Bp as well, no risk of hyponatremia in case with normnatremia at initial visit.

In recent studies use ofempagliflozin as monotherapy or add on consistently resulted in significant reductions in systolic blood pressure (SBP) from baseline at 24 weeks ranging from - 2.9 to - 5.2 mm Hg ($p \leq 0.032$) (3-6,9).Similar findings wereobserved for diastolic blood pressure (DBP). In cohorts of patients with T2DM and hypertension, empagliflozin reduced pulse pressure and SBP compared with placebo, particularly in subgroups of patients with advanced age (≥75 years) and high baseline SBP (>140 mm Hg) (11).empagliflozin treatment also reduced arterial stiffness and vascular resistance in both cohorts (13).

Table 2: Chemical profile of patient's character at the Center

Investigation	**No. (%)**
HBA1c (8 - 15 g %)	10.3 ± 1.83
8 - 10 g%	20 (50%)
> 10g%	20 (50%)
S. Na	S Na 131-154 (140 ± 4.59)
135- 140 Normal	39 (97.5%)
>140 Abnormal	01 (2.5%)
S. Creatinin	0.3 - 1.5 (0.83 ± 0.25)
Normal	38 (95%)
Abnormal	02 (5%)
e GFR Chronic Kidney Disease	1.23 ± 85.5
Stage 1	23 (57.5%)
Stage 2	14 (35%)
Stage 3a	02 (5%)
Stage 3b	01 (2.5%)
History of Urinary Tract Infection	

Yes	23 (57.5%)
No	15 (37.5%)

In this study as all our patients were received statin either indicated forprimary or secondary prevention for CVD, there were no changes in TC,LDL-C,HDL-C, and TGA levels with use of empagliflozin.Small increases in high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides with empagliflozinhave been reported in a pooled analysis of four placebo-controlled trials of empagliflozin, with no change in the LDL-C/HDL-C ratio (13).In a pooled analysis, empagliflozin was reported to reduce blood uric acid levels compared with placebo, with reductions of -0.6 mg/dl for both doses of empagliflozin compared with placebo14,in our study also, Uric acid levels were high at starting with 6.42±1.3, that were significant reduced at 6 week to 5.95± 1.08.Albuminuria is a recognizedmarker for indicating glomerular damage15,after exclusion other causes of albumin-urea controlled B Pr, treat UTI, repeat sample for albuminurea were 55.25±104.72 at initiation of study ,were reduced in most our patients with 19.02±7.76 at 6 week of study that also shown in other studies. Empagliflozinwas shown to reduce albuminuria in patients with T2DM and renal impairment, with more patients with stage 3 CKD on empagliflozin 25 mg converting from macroalbuminuria or microalbuminuria at baseline to microalbuminuria or no albuminuria, respectively (16).

There were initial trainset increase in S Cr ,decline in e -GFR ,that observed in some group of patients with eventually reduction in S Cr lower than base line value ,that also observed with use of ACI ,may signify to nephron-protective form diabetes kidney disease. The base line S Cr (with mean 0.3 ±0.25),there were small raise to (0.94± 0.13) after 6 week of treatment (p = 0.007 from 0.03 to 0.19) with improvement in renal function that assessed by improvement in e GFR. It is noteworthy that there were initial raise in S Cr to about 30% above base-line in some patients (4 out of 40,10%) within first two weeks of treatment that followed immediate with reduction to normal,with over- all improvement in e-GFR over all the risk of raised S Cr not change renal function stage to another advanced stage and SGLT2 (empagliflozin) can be described safely to patients e-GFR above 30 ml/hr.In a study to

evaluate the effectiveness and defense of empagliflozin in patients with T2DM and CKD, empagliflozin 25 mg considerablylowered HbA1c at week 24 (primary endpoint) in patients with stages 2 and 3 CKD compared with placebo ($p<0.0001$), with reductions sustained until week 52 ($p<0.0001$ vs placebo) (16)Also, significant reductions in SBP and body weight were observed in the stage 3 CKD patients at week 24 and week 52 ($p\leq0.0023$). In compare, in patients with stage 4 CKD (e-GFR ≥15 to <30 mL/min/1.73 m^2), empagliflozin 25 mg did not reduce HbA1c versus placebo at week 24 or week 52, whereas changes in SBP and body weight were observed, also deal with alarms of potentialworsening in renal function due to treatment with SGLT2 inhibitors (16). Empagliflozin treatment for 52 weeks resulted in small decreases in eGFR which returned to baseline levels by the end of the 3-week follow-up. Urine albumin to creatinine ratios improved with empagliflozin compared with placebo at week 52 (16).Some empagliflozin studies have shown rise in the frequency of UTIs (asymptomatic bacteriuria, cystitis) in patients taken empagliflozin compared with placebo (7.6%, 9.3%, and 7.6% with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively) (17).Also, patients with a history of chronic or recurrent UTIs, female patients, patients who were ≥75 years of age were more likely to experience a UTI (17). The frequency of treatment withdrawal because of UTIs was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. There have been post-marketing reports of serious UTIs, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin; therefore, patientsshould be assessed clinically and treated prompt, if indicated (17).In present study, the increased incidence of UTIs was controlled by encourage our patient to increase water intake, frequent urine R/E test,and immediate antibiotic description when needed.

In conclusion, the use of SCLT2 inhibitor in patient with uncontrolled DM, high CV risk or established CVD,will benefit by control their hyperglycemia,lower HBA1c,with -out increase risk of hypoglycemia,that will improve the outcome and reduce risk of chronic complications .With reduction in body weight,there were good result and much improve in physical fitness in studied group.Improve in systolicBp will reduce need for poly pharmacy as well as cost of

drugs used. As SGLT2 inhibitors act as nephron -protective with use of it that have a better renal out-come. Empagliflozin when used in high risk group diabetic patients needs good monitoring and close follow up to reduce the risk of hyponatremia,volume depletion and recurrent urinary tract infection

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