Dapagliflozin Improves Cardiovascular Risk Factors in Emirati Diabetic Patients

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Abstract

Dapagliflozin is a sodium-glucose co transporter inhibitor - 2 that proved efficacy in reduction of blood sugar level and control of diabetes through extrusion of glucose in urine. Several studies are available about its cardiovascular as well as renal benefits in diabetic patients. However, data are very limited about its effects in Emirati diabetic patients.

Aim

In this study we aimed at evaluation of dapagliflozin treatment of type 2 diabetic, Emirati patients. Our primary end point was the glycemic control and our secondary end points were its effects on lipids, kidney and cardiovascular risk factors.

Patients & Methods

This is a retrospective cross-sectional study involving 89 diabetic patients who were using dapagliflozin 10 mg tablets once daily as add on therapy for a period of at least 12 months. All patients were type 2 diabetic with age more than 18 years and eGFR (Estimated glomerular filtration rate) more than 60 ml/min/ 1.73 m². Patient exclusion was done if data were not enough, there was a change or adjustment in medication or there was any condition that may affect the assessed variables.

Body weight, height, body mass index (BMI) as per the equation: BMI= weight in Kg/ (height in meters)², sitting blood pressure and heart rate were collected. Fasting plasma glucose, HbA1c and lipid profile and other biochemical parameters e.g. creatinine, blood urea nitrogen (BUN), urine albumin creatinine ratio were traced from medical records of the patients. The Modification of Diet in Renal Disease (MDRD) study formula was used for calculation of eGFR.

Results

This study was conducted on 89 cases; 46 males (51.7%) and 43 females (48.3%). Our study population had a mean age of 62.3 ± 9.4 years and a median duration of diabetes of 15 years.

Both clinical and biochemical parameters were analysed before and at 6 and 12 months of dapagliflozin treatment. Statistical analysis showed significant reduction in Fasting plasma glucose (FPG), HbA1c, Body Mass Index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (p= 0.002, <0.0005, 0.002, <0.0005, <0.0005 respectively).

The median reduction of HbA1c was 0.7 % and 0.9 % at 6 and 12 months, respectively. Reduction of HbA1c directly and positively correlated with baseline HbA1c (p<0.0005). The reduction of these parameters was progressive all through the study time.

Systolic blood pressure (SBP) decreased by a median of 7 and 9 mmHg on the 6th and 12th month of treatment, respectively, while the diastolic decreased by a median of 3 and 6 mmHg. Reduction of blood pressure was not accompanied by increase in heart rate.

The average reduction of body weight was 0.9 kg at 6 months and 0.75 kg at 12 months with significant reduction of BMI (p=0.002). No decline in eGFR and no significant change in lipid profile was observed.

Patients with stage I chronic kidney disease with eGFR less than 90 ml/min/ 1.73 m² showed continuous progressive reduction of HbA1c without deterioration of e GFR. Decline in microalbuminuria particularly at 12-months did not reach a statistical significance (p = 0.174). However, a marked reduction in microalbuminuria was observed in 3 patients of the study group who had significantly high urinary microalbumin at the start of the study.

A significant reduction of C-reactive protein (CRP) at 12 months was observed in patients who had high level at the start of treatment (p=0.011). Rate Pressure Product, was also significantly and progressively reduced all through our study (p <0.0005).

Conclusion

Our data indicate improved cardiovascular risk factor profile in the form of reduction of CRP; BMI, body weight, blood pressure and rate pressure product (RPP)FPG and HbA1c.

Key words: SGL2I; Dapagliflozin; Cardiovascular; HbA1c; Microalbuminuria; CKD.

Received: May 1,2020; Accepted: March 11,2020; Published: March 15,2020

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Introduction

In healthy adults, the kidney filters about 180 grams of glucose daily through the glomeruli, almost ~ 99.9% of this amount is then actively reabsorbed to the circulation by sodium-coupled transport in the proximal tubules. More than 90% of the filtered glucose is reabsorbed by a low affinity, high capacity system controlled by sodium glucose transporter-2 (SGLT2) in the early segment of the proximal convoluted tubule. Reabsorption of almost all remaining filtered glucose is achieved by sodium glucose transporter-1 (SGLT1), a low affinity, high capacity transporter down in the straight segment of the descending proximal tubule. So, in healthy individuals, less than 0.1 gram glucose finds its way into urine [1]. Use of SGLT2 inhibitors aims at reducing the tubular capacity to reabsorb glucose so glucose is lost in urine leading to improvement of glycemic control and relief of glucotoxicity[2]. In diabetic patients, renal threshold for glycosuria is elevated so that, glucose does not pass in urine until plasma glucose is as high as or more than 15 mmol/L. One of the explanation of elevated renal threshold for glycosuria in diabetic patients is the expression and activity of apical SGLT2 and basolateral glucose transporter proteins[3].

A strong rationale for inhibition of SGLT2 as a means to better control glucose levels was dependent on this observation. There are data supporting renoprotective and cardiovascular benefits of SGLT2 including dapagliflozin[4].

Prevalence of obesity in diabetic patients is very high with records up to 50% and its management is an important factor in improving insulin sensitivity and glycemic control[2,5]. Five to ten percent loss of weight can help control of blood sugar and other cardiovascular risk factors and comorbidities[1,6,7].

Among the available antidiabetic medications, metformin may provide modest weight reduction while sulfonylureas, thiazolidinediones and insulin cause weight gain, and dipeptidyl peptidase-4 inhibitors are neutral in respect to body weight[7].

Dapagliflozin is a selective inhibitor of sodium glucose co-transporter 2 (SGLT2) that causes glycosuria and lowers blood glucose levels regardless of insulin sensitivity and β-cell secretory function[8]. Dapagliflozin is associated with reductions in blood pressure and body weight and carries a low intrinsic risk of hypoglycaemia[9]. It also demonstrated cardiovascular (CV) and renal benefits[10,11].

Efficacy of dapagliflozin was tested in comparison with other oral hypoglycemic agents such as metformin, thiazolidinediones, sulfonylureas and dipeptidyl peptidase inhibitors[12,13]. However, data are limited about Emirati population.

In the present study, we investigated the hypoglycemic effect of dapagliflozin as well as its effect on body weight, blood pressure and other possible cardiovascular risk factors.

Materials & Methods

This is a retrospective cross-sectional observational study analyzing data of diabetic patients who received dapagliflozin (10 mg tablet) as add on therapy for 12 months.

The study proposal has been reviewed and approved by the MOHAP Research Ethics Committee, Sharjah (research Approval Reference No. MOHAP/DXB-REC/OON/No. 42 2019). All methods were performed in accordance with the relevant guidelines and regulations of Zulekha Hospital, Sharjah (ZHS). The ethics committee waived the need to obtain informed consent for this study.

Two hundred file of diabetic patients who visited the endocrinology clinic at ZHS from May 2018 to May 2019 were screened. Only 89 patients were eligible for the study. All patients had T2DM age more than 18 years and using dapagliflozin 10 mg tablet as add on therapy for the recent 12 months with no change in other antidiabetic medications and with stable lifestyle pattern all through the study period.

The study is a retrospective one in which dapagliflozin was prescribed as per Food and Drug Administration (FDA), American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and international guidelines. All patients were type 2 diabetic with age more than 18 years and eGFR more than 60 ml/min/1.73 m². Patient exclusion was done if data were not enough, there was a change or adjustment in medication or there was any condition that may affect the assessed variables.

Body weight, height, body mass index (BMI) as per the equation: BMI = weight in Kg/ (height in meters)², sitting blood pressure and heart rate were collected. Fasting plasma glucose, HbA1c and lipid profile and other biochemical parameters e.g. creatinine, blood urea nitrogen (BUN), urine albumin were traced from medical records of the patients. The Modification of Diet in Renal Disease (MDRD) study formula was used for calculation of eGFR[14].

Blood samples were collected from all participants, after an overnight fasting, using plain, EDTA and Lithium Heparin vacutainers. Sera were separated by centrifuging blood at 3,500 rpm for 10 minutes and all samples were immediately processed.

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by Roche diagnostics, Cobas 6000, Modular autoanalyzer using an enzymatic colorimetric method[15,16]. Low-density lipoprotein cholesterol (LDL-C) was directly measured[17]. Blood glucose, C reactive protein (CRP), urine albumin and urine creatinine were determined on the same instrument by enzymatic hexokinase, turbidimetric, immunoturbidimetric & kinetic Jaffe methods; respectively[18]. HbA1c was measured by turbidimetric inhibition immunomassay (TINIA) using COBAS INTEGRA 400 plus machine; Roche Diagnostics. The final result was expressed as HbA1c percent and is calculated from the HbA1c/Hb ratio as follows: HbA1c (%) = (HbA1c/Hb) ×91.5+2.15[19]. ESR was...
measured using Westergren method on Vesmatic 20, Diesse, Italy.

Statistical analysis was done for collected clinical and biochemical data. Any adverse events that occurred during the study were recorded. Two cases of the screened patients stopped dapagliflozin because of recurrent urinary tract infection despite enough treatment by antibiotics according to culture and sensitivity studies. Both cases were postmenopausal females with uncontrolled diabetic state. Four cases were ruled out as they were started on insulin and another 5 patients dropped their follow up in our clinic.

Primary end points
Effect on Hba1c and fasting plasma glucose

Secondary end points
Effect on body weight, blood pressure, heart rate, rate pressure product, eGFR, microalbuminuria, lipid profile and c-reactive protein (CRP).

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (version 25). Qualitative data were expressed as frequency and percentage and McNemar test was used for paired data. Quantitative data were initially tested for normality using Shapiro-Wilk’s test with data being normally distributed if p>0.05. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR) if not. Quantitative data between two groups were compared by Independent-Samples t-test if normally distributed or by Mann-Whitney U test if not. Paired quantitative data were compared by Wilcoxon’s test. Repeated measures were compared by repeated-measures ANOVA if normally distributed or Friedman’s test if not. Pearson’s correlation test for normally distributed data or Spearman’s correlation test if not were used to test for association between quantitative data. For any of the used tests, results were considered as statistically significant if p value ≤ 0.010. Appropriate charts were used to graphically present the results whenever needed.

The following tests were used; Independent-Samples t-Test, Mann Whitney Test, McNemar test, Repeated-measures ANOVA, Friedman’s test, Wilcoxon’s test, Correlation

Results

This study was conducted on 89 cases; 46 males (51.7%) and 43 females (48.3%). Our study population had a mean age of 62.3 ± 9.4 years and a median duration of diabetes of 15 years. At the start of the study, females showed lower Hba1c, total cholesterol (TC), HDL-C and lower ESR in comparison with males [8.35% (7.5-9.9) vs 9.3% (8.25-10.35), p=0.013, 3.8 ± 1.3 mmol/l vs 4.4 ± 0.8 mmol/l, p=0.043, 1.1 ± 0.2 vs 1.3 ± 0.3 mmol/l, p=0.003, 10 (3-17) vs 22 (15.75-39.5), p=0.006 respectively]. Baseline characteristics are shown in table 1.

Both clinical and biochemical parameters were analysed before and at 6 and 12 months of dapagliflozin treatment. Our analysis showed significant reduction in Fasting plasma glucose (FPG), Hba1c, Body Mass Index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (p=0.002, <0.0005, 0.002, <0.0005, <0.0005 respectively). Table 2, Figures 1,2

The median reduction of Hba1c was 0.7 % and 0.9 % at 6 and 12 months, respectively. The median reduction in FPG was 1.65 mmol/l and 2.4 mmol/l at 6 and 12 months of treatment. Table 3 Reduction of Hba1c directly and positively correlated with baseline Hba1c (p<0.0005). The reduction of these parameters was progressive all through the study time. Figures 3,4

Systolic blood pressure decreased by a median of 7 and 9 mmHg on the 6th and 12th month of treatment, respectively, while the diastolic decreased by a median of 3 and 6 mmHg respectively. The reduction of body weight was at an average of 0.9 kg at 6 months and 0.75 kg at 12 months. There was no decline in eGFR and no significant change in lipid profile was observed through the study period. Tables 2,3

Continuous progressive reduction of Hba1c was observed all through the study in patients with stage I chronic kidney disease with eGFR less than 90 ml/min/ 1.73m². No significant change in other parameters was evident in stage I CKD. Table 4

There was an observable decline in microalbuminuria particularly at 12-months, but this did not reach a statistical significance (p=0.174). However, the marked reduction in microalbuminuria was observed in 3 patients of the study group who had significantly high urinary microalbumin at the start of the study. Figure 5

Most interestingly is the significant reduction of C-reactive protein (CRP) at 12 months, in patients who had high level at the start of treatment (p=0.011). Figure 6

Rate Pressure Product, was also significantly and progressively reduced all through our study (p <0.0005). Table 2

Discussion

Dapagliflozin causes a urinary loss of 60-80 grams of glucose per day, which equates to a negative energy balance of 240-320 calories per day, or 0.9-1.3 kg weight loss per month, if this caloric deficit is not compensated by increase in food intake [7,20]. This leads to reduction of blood sugar and recovery from glucotoxicity with improvement of insulin sensitivity and insulin mediated skeletal muscle glucose disposal. So, dapagliflozin helps reduce the risk of diabetes. This reduction of hyperinsulinemia protects many organs from abnormal vasoreactivity, angiogenesis and fibrogenesis [22,23].

In our study, the reduction in Hba1c level was greater than that mentioned by Vasilakou et al (0.7% vs 0.61% and 0.9% vs 0.52% at 6 months and 12 months respectively) [24].

Efficacy of dapagliflozin in Qatari diabetic patients was tested by Al Adawi et al [25]. Study period was 12 months and patients had a mean age of 57.0 ± 9.0 years and a mean baseline Hba1c.
Table 1: Baseline characteristics of the study group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Test statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.3 ± 9.4</td>
<td>63.8 ± 8.2</td>
<td>60.7 ± 10.4</td>
<td>t=1.575</td>
<td>0.119</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>15 (10-20)</td>
<td>15 (10-20)</td>
<td>12 (8-17)</td>
<td>Z= -1.269</td>
<td>0.204</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.4 (26.8-32.7)</td>
<td>15 (10-20)</td>
<td>12 (8-17)</td>
<td>Z= -1.269</td>
<td>0.204</td>
</tr>
<tr>
<td>FPG (mmol/dl)</td>
<td>10.2 (7.9-13.2)</td>
<td>10.3 (8-13.2)</td>
<td>9.9 (7.6-13.1)</td>
<td>Z= -0.433</td>
<td>0.665</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.7 (7.8-10.2)</td>
<td>9.3 (8.25-10.35)</td>
<td>8.35 (7.5-9.9)</td>
<td>-2.481</td>
<td>0.013</td>
</tr>
<tr>
<td>Creatinine (mmol/dl)</td>
<td>79 (64.5-91.25)</td>
<td>77.6 ± 20</td>
<td>83.97 ± 23.6</td>
<td>t= -1.222</td>
<td>0.226</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>131 (119.5-145)</td>
<td>130 (118.5-139.25)</td>
<td>138 (122-149)</td>
<td>Z= -1.800</td>
<td>0.072</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77 (72-82.5)</td>
<td>78 (72.75-80)</td>
<td>76 (70-85)</td>
<td>Z= -0.107</td>
<td>0.915</td>
</tr>
<tr>
<td>Urea (mmol/dl)</td>
<td>5.4 (4.1-8.4)</td>
<td>6.8 (4.1-8.6)</td>
<td>4.9 (3.8-6.35)</td>
<td>Z= 0.159</td>
<td>0.0.165</td>
</tr>
<tr>
<td>ACR (Albumin creatinine ratio)</td>
<td>13 (51.-24.5)</td>
<td>8.7 (5.4-20.1)</td>
<td>14.7 (5-45.1)</td>
<td>-1.569</td>
<td>0.117</td>
</tr>
<tr>
<td>T-C (mmol/dl)</td>
<td>4.1 ± 1.1</td>
<td>4.4 ± 0.8</td>
<td>3.8 ± 1.3</td>
<td>t=2.085</td>
<td>0.043</td>
</tr>
<tr>
<td>LDL-C (mmol/dl)</td>
<td>13 (51.-24.5)</td>
<td>2.2 (1.5-2.8)</td>
<td>1.8 (0.99-2.6)</td>
<td>Z= -1.046</td>
<td>0.296</td>
</tr>
<tr>
<td>HDL-C (mmol/dl)</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>t=3.122</td>
<td>0.003</td>
</tr>
<tr>
<td>Triglycerides (mmol/dl)</td>
<td>1.21 (0.88-1.7)</td>
<td>1.23 (1.0-1.9)</td>
<td>1.18 (0.80-1.53)</td>
<td>Z= -0.857</td>
<td>0.391</td>
</tr>
<tr>
<td>TSH uiu/ml</td>
<td>1.93 ± 1.02</td>
<td>2.01 ± 0.96</td>
<td>1.82 ± 1.1</td>
<td>t=0.683</td>
<td>0.497</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>18 (8-29)</td>
<td>22 (15.75-39.5)</td>
<td>10 (3-17)</td>
<td>Z= -2.747</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± SD and compared by Independent-Samples t-Test if normally distributed * or Median (IQR) and compared by Mann Whitney Test if not normally distributed **
Baseline characteristics were not statistically significantly different between male and female patients except for T-C, HDL-C, and ESR (all were significantly higher in male).
Abbreviations: BMI: Body Mass Index; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; SBP: Systolic Blood Pressure; DBP:Diastolic Blood Pressure; T-C: Total Cholesterol; LDL-C:Low-density lipoprotein Cholesterol; HDL-C:High-density lipoprotein Cholesterol; TG:Triglycerides; ESR:Erythrocyte sedimentation rate

**Figure 1:** Progressive decline in A1c in the study group
This figure shows the decline in HbA1c in the study group (n=87).
This figure shows that the decline in HbA1c over time occurs in patients with and without CKD at baseline.

Data are presented as *Median (IQR) and compared using Friedman’s test for 3 measures or Wilcoxon’s test for 2 measures or as **mean ± SD and compared by Repeated-measures ANOVA. Pairwise comparisons are presented as letters. Pair with similar letters = insignificant Difference while pair with different letters = significant difference. This table showed a statistically significant difference over time as regard to BMI: Body Mass Index, FPG: Fasting plasma glucose, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure and HbA1c: Glycated hemoglobin.
These two scatterplots for correlation between baseline HbA1c and its reduction in 6- and 12-months shows a statistically significant positive correlation ($r_s=0.514$ for 6-months reduction and 0.690 for 12-months reduction, $p<0.0005$) which means that the higher the baseline HbA1c, the higher the reduction in HbA1c over 6- and 12-months. The median reduction (IQR) in HbA1c was 0.7 (0.2-1.2) in 6-months and 0.9 (0.5-1.8) in 12-months.

Table 3: Shows the median change in different variables at 6 months and 12 months of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in 6-months</th>
<th>Change in 12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/l)</td>
<td>1.65</td>
<td>2.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>0.9</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>0.3</td>
<td>0.35</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>0.76</td>
<td>1.41</td>
</tr>
</tbody>
</table>

This table showed the median reduction in FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, weight and BMI: Body Mass Index and the median increase in eGFR which occurred in treated patients in 6- and 12-months.
This figure shows a decline in ACR: Albumin creatinine ratio level particularly at 12-months, though this did not reach a statistical significance. A larger study on patients with microalbuminuria is justified to study the possible improvement over time which was clearly observed in some of our patients as shown in the figure.

Figure 6: shows significant change in CRP: C-Reaction protein at 12 months of treatment of patients who initially had high CRP.

In Manuel’s study, body weight decreased by 1.7 kg with the 5-mg dapagliflozin and 2.2 kg with the 10-mg compared with placebo [29].

In our study, the average reduction was about 0.9 kg after 6 months and 0.75 kg at one year. Inability to lose more weight may be explained by lifestyle and dietary habits of patients in this age and in this region with high prevalence of diabetes.

Reduction of body weight especially by loss of visceral fat further improves insulin sensitivity and decreases blood sugar and HbA1c besides the glucose losing in urine [20,24].

The cardiovascular and blood pressure lowering effect of dapagliflozin was suggested to be due to a significant reduction of tissue sodium content as demonstrated by Karg, et al after 6 weeks of dapagliflozin treatment [30]. Decrease in body sodium is of special significance in type 2 diabetic patients who are known to retain more sodium in their bodies and are prone to
Table 4: Comparisons of repeated measures of HbA1c, BMI, eGFT and serum creatinine:

<table>
<thead>
<tr>
<th>Measure</th>
<th>At baseline</th>
<th>At 6-months</th>
<th>At 12-months</th>
<th>Source</th>
<th>F value</th>
<th>Partial h²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CKD</td>
<td>No CKD</td>
<td>CKD</td>
<td>No CKD</td>
<td>CKD</td>
<td>No CKD</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9 ± 1.7</td>
<td>8.9 ± 1.5</td>
<td>8.2 ± 1.5</td>
<td>7.9 ± 1.3</td>
<td>7.7 ± 1.2</td>
<td>7.4 ± 0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td></td>
<td></td>
<td>Time</td>
<td>38.589</td>
<td>0.373</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td></td>
<td>Time*CKD</td>
<td></td>
<td></td>
<td></td>
<td>0.336</td>
<td>0.005</td>
<td>0.666</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 ± 6.8</td>
<td>31.4 ± 6</td>
<td>28.7 ± 6.9</td>
<td>31.1 ± 6.2</td>
<td>28.5 ± 7.1</td>
<td>30.8 ± 6.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td></td>
<td></td>
<td>Time</td>
<td>3.102</td>
<td>0.048</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Time*CKD</td>
<td></td>
<td></td>
<td></td>
<td>0.115</td>
<td>0.002</td>
<td>0.806</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>69.4 ± 14.9</td>
<td>125.1 ± 37.8</td>
<td>72.2 ± 20.7</td>
<td>126.4 ± 33</td>
<td>70.9 ± 20</td>
<td>128 ± 44.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td></td>
<td></td>
<td>Time</td>
<td>0.37</td>
<td>0.007</td>
<td>0.692</td>
</tr>
<tr>
<td></td>
<td>Time*CKD</td>
<td></td>
<td></td>
<td></td>
<td>0.135</td>
<td>0.003</td>
<td>0.874</td>
</tr>
<tr>
<td>Serum creatinine (mmol/dl)</td>
<td>95.4 ± 19.4</td>
<td>69.9 ± 17.1</td>
<td>93.5 ± 24.2</td>
<td>67.9 ± 16.7</td>
<td>94.1 ± 21.8</td>
<td>68.8 ± 17.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td></td>
<td></td>
<td>Time</td>
<td>0.517</td>
<td>0.01</td>
<td>0.574</td>
</tr>
<tr>
<td></td>
<td>Time*CKD</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td>0</td>
<td>0.997</td>
</tr>
</tbody>
</table>

Partial h² = Partial eta square (a measure of effect size). P value is by repeated measures ANOVA.

Our cohort was subdivided into two groups according to the results of basal eGFR: CKD group with eGFR < 90 ml/min (n=23) and no CKD group with eGFR ≥ 90 ml/min (n=44). CKD group has statistically significant older age (65.6 ± versus 59.7 ± 7.4 years, t= -3.662, p=0.01) but there was no significant difference in sex distribution; male/female = 14/9 in CKD group and 21/23 in no CKD group (c²=1.046, p=0.307).

This table showed that only HbA1c had statistically significant change (decrease) over time with no interaction with group. It shows also a tendency to significant reduction in BMI: Body Mass Index but this did not reach statistical significance (p=0.07).

cardiovascular complications [30, 31].

SGLT-2 inhibition blocks both glucose and sodium reabsorption in the proximal tubular cells. This leads to osmotic diuresis and natriuresis with reduction of both systolic and diastolic blood pressures and weight loss as well. Reduction of blood pressure may be also related to weight loss [31,32].

Comparable to reports of other studies, the use of dapagliflozin in our population was associated with a significant reduction of both systolic (7mmHg and 9 mmHg at 6 and 12 months respectively, p <0.0005) and diastolic blood pressure (3 mmHg and 6 mmHg at 6 months and 12 months respectively, p<0.00005) [33-36]. Heerspink et al reported changes in HbA1c, systolic blood pressure (SBP) and body weight of −0.5% (95% CI −0.7, −0.3) and −3.5 mmHg (95% CI −5.9, −1.0) and −0.76 kg (95% CI −1.27, −0.26) respectively [37].

It is worthy mentioning that reduction of blood pressure was not associated with increase in heart rate. Glucose-lowering treatments that reduce body weight and SBP without affecting heart rate are of special value in diabetic patients [38]. This is particularly important in patients with chronic kidney disease (CKD). Studies indicate that higher resting heart rate is a risk factor for end-stage renal disease (ESRD) and CKD-related hospitalizations [39].

We also report a significant reduction in the rate pressure product (RPP) at 6 and 12 months of treatment (p < 0.0005). Rate Pressure Product is used to determine the energy requirement and myocardial oxygen consumption expressed as the product of SBP and resting heart rate divided by 100 (RPP = SBP x HR/100) [37,38].

Reduction in RPP indicates decreased cardiac work and oxygen consumption at rest. This may take part in the justification of the improved quality of life and decreased hospitalization in heart failure patients and reduced incidence of type 2 myocardial infarction in patients using dapagliflozin as mentioned in both DEFINE and DECLARE-TIMI 58 studies [40-43].

It was found that dapagliflozin treatment suppressed atherogenic small dense LDL-C and increased HDL-C [41,45]. In our study, we did not notice a significant effect of dapagliflozin on lipid profile.

Different studies reported improved endothelial function, [45] reduction of arterial stiffness and renal resistive index in type 2 diabetic patients with use of dapagliflozin [46-51]. Improvement of endothelial function and improved parameters of early vascular remodeling may be interpreted in our study by the significant reduction in CRP in patients who initially had high level before starting treatment.

Approximately 30–40% of diabetic patients have chronic kidney disease, drug safety in this group of patients is important during management of diabetes [51].

Both Heerspink et al [52] and Kohan et al [53] found reduction of microalbuminuria. In his study, Heerspink found a reduction by at least 30% in 50% of patients who had microalbuminuria. Both authors suggested that the change in microalbuminuria was independent of changes in glycemic control. In our study, we did not find significant reduction in microalbuminuria, although marked reduction was observed in few patients who already had...
significantly high microalbumin in urine. Figure 5

Similar to our observation, Manuel et al [29] showed no significant difference in eGFR or albumin/creatinine ratio at 24 weeks of treatment, after adjustment for HbA1C, SBP and body weight. The same observation was also demonstrated by Fioretto et al [54].

Studies which explored the efficacy and safety of SGLT2 inhibitors in patients with impaired kidney function have predominantly included patients with Stage 3 CKD [eGFR: 30–60 mL/min/1.73 m²], and have demonstrated that the glucose-lowering efficacy of SGLT2 inhibitors in these patients is diminished compared with patients with normal kidney function[55]. Claire et al did not find a significant change in HbA1c in patients with type 2 diabetes having Stages 3b–4 CKD, but there was a decrease in urinal albumin creatinine ratio, blood pressure and body weight to a clinically meaningful extent [56–58].

In our study, in patients with mild reduction of eGFR < 90ml/min/1.73m² (stage 1 CKD), dapagliflozin improved blood sugar and HbA1c level over a period of one year without further deterioration of eGFR (p=0.806).

Few side effects were reported such as constipation, abdominal distension. Only 2 patients stopped the medicine because of recurrent urinary tract infection, both of them were postmenopausal females above 60 years of age.

In conclusion, our data indicate an improved cardiovascular risk factor profile in the form of reduction of CRP, body weight,BMI, blood pressure, RPP Fpg, and CRP/HbA1c. Effect of dapagliflozin on cardiovascular risk factors was previously described in detail in a real-world primary and diabetologist care setting and also in the CVD-REAL Nordic study [59].

Our study has several limitations due to its retrospective design, including a small sample size and lack of more informative metabolic parameters for obesity, insulin resistance, and β-cell function. Therefore, further studies are needed that include abdominal circumference, dual-energy X-ray absorptiometry, and body composition.

Disclosure

The authors report no conflict of interest in this work.

References

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