Observational Study to Evaluate Effectiveness of Adding Empagliflozin to Uncontrolled Type 2 Diabetes Patients Who Were Uncontrolled On Metformin Rather Than Up Titrating the Metformin Dose

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ABSTRACT

Aim: The main objective of this prospective observational study to evaluate effectiveness of adding empagliflozin to uncontrolled type 2 diabetes patients who were uncontrolled on metformin rather than up titrating the metformin dose.

Material & Method: This was a prospective observational study conducted among 90 patients who had qualified as per the inclusion and exclusion criteria. After inclusion patients were divided into two groups one group 10 mg Empagliflozin OD were added with 1000 mg metformin OD (N=45) and in other group metformin were up titrated to 2000 mg OD (N=45) as this is considered as maximum tolerable dose of metformin.

Result: There was a significant weight reduction in Empa + Met group which was as high as 1 kg over 24 weeks’ time frame. Despite on adequate anti-hypertensive management in both the group further statistically significant reduction in both SBP and DBP were observed in Empa+Met group (10.2±3.5 mmHg and 7.2±2.6, respectively) which was not with Met group. There were a further statistically significant reduction in total cholesterol; triglyceride and LDL Cholesterol despite the group were on optimal dosage of lipid lowering therapy.

Conclusion: Empagliflozin 10 mg is a potent glucose lowering agent and should be added to patients who were initially uncontrolled with metformin monotherapy rather than up titrating metformin dose. Empagliflozin offer better pleotropic benefits when added as second line therapy to metformin.

Keywords: Empagliflozin, uncontrolled type 2 diabetes patients, metformin

INTRODUCTION

Diabetes, a slowly growing epidemic, is becoming a growing burden to the nation’s health and economy [1]. Efforts to curb the complications as well as limit the disease by intense management was met with several challenges earlier, including metabolic side effects, fatal complications and sometime raised overall mortality [2-5].

Diabetes and its complications are one of the leading causes of mortality and morbidity all over the world. As the disease and its complications are becoming rampant, a stringent management plan is essential [6]. A 1% increase in the glycated hemoglobin (HbA1c) level is associated with can increase of 18% in the risk of cardiovascular (CV) events. Apart from that, can increase of 12-14% in the risk of death and can increase of 37% in the risk of retinopathy or renal failure is also noted, implying a definite need to keep blood sugar in check [6,7].

Glycemic control has always been a delicately balanced act. The patients not only needs to maintain a euglycemic state but also should be educated enough to make or revise decision strategies, volitional control and the sense to avoid hypo and hyperglycemia. Metformin is a biguanide drug, currently recommended as the first line of therapy in most patients with type 2
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diabetes \cite{8-10}. Its advantages include low risk of hypoglycemia, modest weight loss and low cost. The sodium glucose cotransporter 2 (SGLT2) inhibitors reduce hyperglycemia by inhibiting the SGLT2 transporter found on the proximal convoluted tubule of the nephron \cite{11-14}. This leads to loss of a significant proportion of the filtered glucose by means of glycosuria. Recently, duel inhibitors have been developed, that inhibit not only SGLT2, but also SGLT1, which is responsible for glucose absorption \cite{15}.

The main objective of this prospective observational study to evaluate effectiveness of adding empagliflozin to uncontrolled type 2 diabetes patients who were uncontrolled on metformin rather than up titrating the metformin dose.

**METHODS AND MATERIALS**

This was a prospective observational study conducted among 90 patients who had qualified as per the inclusion and exclusion criteria. Initially 108 patients were identified but 18 patients were excluded from the study as 13 were lost in follow-up and 5 were irregular in follow-up checkup. The main inclusion criteria were type 2 diabetes patients who were ≥ 18 years of age and HbA1c >7%, were on metformin monotherapy 1000 mg and ready to give informed consent. Patients who were having documented micro and macro vascular complications, pregnant or lactating women, patients with impaired liver function were excluded from the study.

After inclusion patients were divided into two groups one group 10 mg Empagliflozin OD were added with 1000 mg metformin OD (N=45) and in other group metformin were up titrated to 2000 mg OD (N=45) as this is considered as maximum tolerable dose of metformin. Demographic details like age, gender, duration of diabetes, weight, BMI and other medication detailed were collected through a predesigned proforma. Blood pressure was measured at baseline and during each follow-up by a clinic manual BP measurement instrument (AccuSure Mercury Sphygmomanometer). Serological test like FBS, PPBS, HbA1c, lipid profile (total cholesterol, triglyceride, LDL cholesterol and HDL cholesterol), blood urea and serum creatinine were evaluated at baseline and in each follow up.

Microsoft excel sheet were used to collect the data thereafter with help of SPSS 22.0 data were analysed. A descriptive bivariate analysis was performed; for the chi-squared distribution, significance was assumed to be <0.05.

**RESULT**

Demographic details were listed in table 1. It was observed that the demographic characters were almost similar in both the groups. A good percentage of patients in both the group were having similar co morbidity like hypertension and dyslipidemia. Maximum numbers of patients in both the group were on anti-hypertensive and lipid lowering drugs.

Table 1: Demographic characteristic of the participants in both group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Empa + Met Gr (N=45)</th>
<th>Met Gr (N=45)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>52.8±7.2</td>
<td>53.2±6.9</td>
<td>0.671</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>23/22</td>
<td>21/24</td>
<td>0.945</td>
</tr>
<tr>
<td>Duration of Diabetes (Years)</td>
<td>2.1±1.3</td>
<td>2.3±0.8</td>
<td>0.037</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>30.4 ±5.3</td>
<td>30.5 ±5.0</td>
<td>0.742</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>83.8 ±19.8</td>
<td>83.0 ±19.1</td>
<td>0.385</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128.4 ±15.8</td>
<td>127.0 ±13.7</td>
<td>0.583</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.3 ±9.4</td>
<td>78.5 ±8.1</td>
<td>0.491</td>
</tr>
<tr>
<td>No of patients on hypertension medication (%)</td>
<td>31 (69%)</td>
<td>28 (62%)</td>
<td>0.854</td>
</tr>
<tr>
<td>No of patients on lipid lowering drugs (%)</td>
<td>38 (84.4%)</td>
<td>37 (82.2%)</td>
<td>0.985</td>
</tr>
</tbody>
</table>

Table 2 demonstrates the changes in parameters under study over 24 weeks’ time frame in both the groups. There was a significant weight reduction in Empa + Met group which was as high as 1 kg over 24 weeks’ time frame. Despite on adequate
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anti-hypertensive management in both the group further statistically significant reduction in both SBP and DBP were observed in Empa+Met group (10.2±3.5 mmHg and 7.2±2.6, respectively) which was not with Met group.

Table 2: Changes in parameters among two studied group from baseline to 24th week

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Empa + Met Gr (N=45)</th>
<th>Met Gr N=45)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (Kg)</td>
<td>83.8±19.8</td>
<td>82.3±9.8</td>
<td>0.001</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>161.2±18.27</td>
<td>121.86±15.25</td>
<td>0.001</td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td>244.6±39.54</td>
<td>184.79±28.56</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.66±0.87</td>
<td>7.50±0.56</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128.4±15.8</td>
<td>118.2±9.3</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.3±9.4</td>
<td>72.1±6.7</td>
<td>0.001</td>
</tr>
<tr>
<td>T. Cholesterol (mg/dl)</td>
<td>193.76±37.94</td>
<td>176.83±31.26</td>
<td>0.001</td>
</tr>
<tr>
<td>S. Triglycerides (mg/dl)</td>
<td>173.3±31.12</td>
<td>159.36±23.55</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>131.3±28.21</td>
<td>119.41±23.55</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>41.52±9.36</td>
<td>42.05±6.22</td>
<td>0.142</td>
</tr>
<tr>
<td>Blood Urea</td>
<td>29.4±5.04</td>
<td>26.96±4.18</td>
<td>0.3079</td>
</tr>
<tr>
<td>S. Creatinine</td>
<td>0.91±0.05</td>
<td>0.88±0.04</td>
<td>0.5826</td>
</tr>
</tbody>
</table>

Empa + Met group has demonstrated a higher impact on lipid profile as compare to metformin group which listed in table 2. There were a further statistically significant reduction in total cholesterol, triglyceride and LDL Cholesterol despite the group were on optimal dosage of lipid lowering therapy.

Figure 1:HbA1c Reduction over 24 weeks in two groups

Figure 2:FBG and PPG reduction in both the group after 24 weeks

DISCUSSION

The role of metformin in the treatment of type 2 diabetes is already well established. Its multitude of actions and good safety profile has made it the most prescribed oral anti diabetic drug. Recent literature and ongoing studies of its benefits on a wide variety of risk factors and complications of diabetes (such as lipid profile, body weight, cardiovascular risk, antiaging and antineoplastic) are providing promising results. The potential of this safe and simple drug to shape the future of diabetes should not be underestimate. Sodium glues transporter 2 (SGLT2) inhibitors act by reducing renal glucose reabsorption and lowering blood glucose through glycosuria. EMPAREG OUTCOME and CANVAS programs are two post marketing CV outcome studies with the SGLT2 inhibitors empagliflozin and canagliflozin, respectively which showed significant improvements in the 3 point MACE with these agents. 

The effect of empagliflozin was found with the EMPAREG OUTCOME study which randomized 7,200 T2DM patients with CV disease, A dose of 10 mg
to 25 mg/day empagliflozin or placebo was administration and the patients were followed for 3.1 years. More than 75% treatment of the CV risk of patients in EMPAREG OUTCOME trial included the following received statin, more than 95% received antihypertensive therapy and about 90% received anticoagulant/antiplatelet drugs [20]. Though, empagliflozin did not affect the onset of nonfatal MI and stroke, it seemed to significantly reduce hospitalization for heart failure [22]. Rapid divergent rates of the MACE, mortality and heart failure hospitalization between the empagliflozin and placebo groups was a notable feature of this trial, recorded within the first 6 months after randomization.

Current study has addressed very pertinent clinical question that whether should clinician up titrate the monotherapy or add second therapy. It this study it was clear that adding empagliflozin to metformin monotherapy not only help the patients to achieve better glycemic control than compare to high dose titration but also offer better pleotropic benefits like reduction in weight, BMI, blood pressure and lipid profile. Despite on adequate antihypertensive management in both the group further statistically significant reduction in both SBP and DBP were observed in Empa+Met group (10.2±3.5 mmHg and 7.2±2.6, respectively) which was not with Met group. There were a further statistically significant reduction in total cholesterol; triglyceride and LDL Cholesterol despite the group were on optimal dosage of lipid lowering therapy.

CONCLUSION

Empagliflozin 10 mg is a potent glucose lowering agent and should be added to patients who were initially uncontrolled with metformin monotherapy rather than up titrating metformin dose. Empagliflozin offer better pleotropic benefits when added as second line therapy to metformin. The use of SGLT2i is a novel approach to glycemic control and is accompanied by multiple demonstrable cardio-metabolic and renal benefits beyond its glucose-lowering effect.

REFERENCES

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