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How can We Use Empagliflozin as an Adjuvant in Reducing Required Need of Insulin in Type 1 Diabetes along with Lowered HbA1c, Weight without Fear of DKA - A Mini Review

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ABSTRACT

Therapy of persons having Type1 Diabetes mellitus (T1DM) has advanced, much more from the time when insulin was given to a child with T1DM. Increased years of life spent, with associated chronic complications like cardiovascular disease (CVD) and renal diseases at older age group and Diabetic ketoacidosis (DKA) and hypoglycemia at a younger age are the major challenges. People suffering from T1DM in routine daily practice have to bear the massive alterations in glucose levels that is frustrating and depressing but further markedly enhancement of their body weight with overweight in 42% and obesity in 23.8% of people who have T1DM. Empaglifozin is an SGLT 2 Inhibitor which is in common with other agents in this class and decreases the elevated blood glucose levels by inhibiting SGLT2, that is the main transporter needed for reabsorption of glucose On the basis of 2 phase 2 and phase 3 studies namely EASE trials were evaluated and demonstrated definite advantage of use of Empaglifozin as an adjuvant to insulin in reducing blood glucose levels, Hb A1c, weight, need for insulin dosages. The only worrying problem remains is the fear of unrecognized Diabetic ketoacidosis (DKA) in view of clinicians not accustomed to dealing with DKA with such lower blood glucose levels like 250 mg that has been named by FDA as "euglycemic DKA." This can be overcome by training the patient along with treating physician, how to suspect, recognize and treat it in time. Advantage of EASE was the usage of very low dosage of Empaglifozin 2.5 mg as well that is not the therapeutic dosage but can help physicians to work out the best dosage and plan to recognize, prevent and treat DKA to prevent any mishap as occurred in 25 mg arm of EASE-2, 25 mg arm. Till date Empaglifozin is not approved for T1D treatment but it holds promise to gradually overcome the little lacunae left and try to improve life of T1DM subjects in aiding in reducing insulin dosage, decrease HbA1C, increased variability of glucose prevention along with reduce weight.

KEYWORDS

T1DM; SGLT 2 inhibitor; Empaglifozin; EASE trials; Hb A1c; Weight loss ; Insulin dosages reduction; Euglycemic DKA

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1. INTRODUCTION

Therapy of persons having Type1 Diabetes mellitus (T1DM)has advanced , much more from the time when insulin was given to a child with T1DM.Improvements in the insulin injections , especially innovative insulin analogs, insulin pens, insulin pumps, but also the advances of glucose monitoring has drastically improved treatment. There is a major change in our thought process regarding what having T1DM meant in the last century than in the present one. Despite the problems which keep getting encountered by the T1DM subjects along with the health care personnel attending him or her, there is an enhanced morbidity as well as mortality [1]. Increased years of life spent, with associated chronic complications like cardiovascular disease (CVD) and renal diseases at older age group and Diabetic ketoacidosis (DKA) and hypoglycemia at a younger age as major challenges. People suffering from T1DM in routine daily practice have to bear the massive alterations in glucose levels that is frustrating and depressing but further markedly enhancement of their body weight with overweight in 42% and obesity in 23.8% of people who have T1DM [2]. These requirements that have not been tackled have initiated the lookout for a more lucrative adjuvant treatments, especially for achieving a >stability of glucose regulation, with <chance of hypoglycemia and <enhancement of weight. Till now only one adjuvant treatments has been approved by FDA with none in Europe, i.e. pramlintide. In USA as well pramlintide use is not high in view of need for injections at lot of times in a day at meal hours and especially due to adverse effects of nausea and vomiting. A systematic review and meta-analysis of the studies pointed that though Hb A1c reduction was obtained, the adverse effects like nausea and vomiting were for real and further hypoglycemia was very much recurrent [3].

Many physicians have tried the addition of metformin to insulin therapy in many T1DM as off label therapies , various experimental studies as well as real world findings suggested little weak or moderate enhancements in glycemic regulation as well as body weight [4]. In the beginning with the advent of glucagon like peptide 1 (GLP1) receptor agonists there was a lot of faith following short term studies .The Adjunct program verified the efficacy on good effects on weight, but also showed that glucose decrease though marked was just for short duration, and associated with marked escalation of severe hypoglycemia and >chances of ketosis [5, 6].

2. METHODS

Thus we conducted a mini review regarding use of SGLT2 Inhibitors utilizing the PubMed engine with the Mesh terms like T1DM; Insulin; Adjuvants to insulin; SGLT2 Inhibitors; Empagliflozin; Canagliflozin; Dapagliflozin; DKA; Hypoglycemia; Weight loss; Insulin dose reduction

3. RESULTS AND DISCUSSION

We found a total of 368 articles out of which we chose 28 articles for this mini review. No meta-analysis was done.

3.1 Role of use of SGLT 2 inhibitors as adjuvant therapies in T1DM

Sodium-glucose cotransporter 2(SGLT2) inhibitors, remain an attractive choice for starting initial therapy in Type 2 Diabetes mellitus (T2DM). Their mechanism of action is insulin-independent, i.e. by blocking the sodium and glucose transporters in kidney (SGLT1 and SGLT2) and in gut (SGLT 2). SGLT 2 inhibition leads to increasing the urinary excretion of glucose [7]. This occurs via inhibiting reabsorption of glomerular filtered glucose that takes place in the proximal convoluted tubules of the kidney, and hence reduces glucose, stimulates loss of weight and decrease in systolic blood pressure (BP).What is to be highlighted that these drugs do not require beta cells for their glucose decreasing action and hence can be

utilized at all stages of Type2 Diabetes mellitus (T2DM), even on combining with insulin. This profile has brought them in limelight regarding any newer decisions made by American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [7].

Along with that weight reduction and lowering of blood pressure (BP) occurs in contrast to placebo thus they, remain an attractive choice. Earlier we have reviewed the importance of starting SGLT 2 Inhibitors as initial agents in starting combined therapy in T2DM and further explored the Cardiovascular Outcome Trials (CVOT) advantages of Empaglifozin, canaglifozin, and dapagliflozin in the form of empa reg, canvas and declare respectively [8-12].From the initial days, it was clear that these drugs would further lower blood glucose levels in separate kind of diabetes especially T1DM. Short term work showed massive decrease in Hb A1C reduction in insulin requirements for regulating glucose, no enhancement of severe hypoglycemia along with the anticipated body weight loss [13].

3.2 T1DM and empagliflozin

For the T2DM 3 SGLT2 agents have got the approval of both FDA and EMA, namely canagliflozin, dapa gliflozin and Empagliflozin. Another SGLT2 inhibitor, ertugliflozin has got approval recently.

Empaglifozin is an SGLT 2 Inhibitor which is in common with other agents in this class and decreases the elevated blood glucose levels by inhibiting SGLT2, that is the main transporter needed for reabsorption of glucose from the glomerular filtrate and hence increases urinary excretion of glucose. It gets absorbed rapidly, reaching peak levels following roughly 1.33 h - 3.0 h. Its average half-life varied from 5.6 h - 13.1 h in a single increasing dosage study and from 10.3 h to 18.8 h in multiple dose studies [14].

For T1DM in a single arm pilot study for 8 weeks in subjects having T1DM. Empagliflozin was utilized along with insulin and as an additive it caused marked decreases in Hb A1C [15], after which a development method known as EASE (Empagliflozin as adjunct to insulin therapy) was formatted.

Initially EASE 1 trial was made to evaluate the pharmacological dynamics, effectiveness and how safe Empagliflozin was when used along with insulin in T1DM subjects [16]. This was a double-blind placebo regulated phase II study where 75 T1DM subjects were enrolled. These patients had a bad regulation of glycaemia having a mean Hb A1C $\geq$7.5% to $\leq$10.5%. Once/day Empagliflozin 2.5 mg; Empagliflozin 10 mg or Empagliflozin 25 mg was given to these patients in addition to a basal bolus insulin therapy. Initially, in the 1st 7 days a stable insulin dose was given. Following that the physicians could adjust the insulin dose for obtaining proper glycaemia regulation. Marked enhancement of 24 h glucose excretion was caused by Empagliflozin on day 7 and day 28, which led to Hb A1c decrease to -0.49% from -0.35% on 28th day as well as weight loss from -1.5 kg - 1.9 kg with total/day insulin decrement at 28th day from -0.07 U/Kg to -0.09 U/Kg. Throughout the whole study, hypoglycemic episodes were much less with Empagliflozin as compared to placebo. Genital infection was not reported at all and only 1 urinary tract infection (UTI) case was seen in a female subject on 25 mg Empagliflozin. Though encouraging results as far as effectiveness as well as safety profile were concerned as an additive to insulin in pts. with T1DM, power of this experiment had its limitations in view of small time period as well as sample size being little .

Further after the above pilot study 2 big double-blind placebo regulated phase III trials namely EASE-2 where Empagliflozin 10 mg in 243 subjects and 25 mg in 244 subjects, with placebo in 241 subjects were administered for 52 weeks [17]. Aim of this EASE-2 was to reexamine the effectiveness as well as safety profile of 10 mg and 25 mg doses along with a special, lower dose 2.5 mg in the

form of adjunct to markedly enhanced insulin in T1DM subjects. Baseline properties were equalized in all therapy groups (respectively, EASE 2 and 3; 45-53 yrs. DM period 22.5 yrs. - 21yrs., Hb A1C 8.1% - 8.2% mean overall insulin dose 0.7 unit/kg and BMI 29.1 Kg/m^2 - 28.2 Kg/m^2).

Statistically significant Hb A1C decreases following 26 weeks was observed in all Empagliflozin dosages in EASE 2 and 3. Maximum placebo adjusted decreases with Empagliflozin 10 mg (-0.45% to -0.54%) and 25 mg (-0.52 to -0.53%) dosages were seen but even with small dose Empagliflozin 2, 5 mg Hb A1C decreases in a significant manner i.e. -0.25% was observed.

This action of Empagliflozin was maintained at 52 weeks in the EASE-2 study. Additionally, Empagliflozin caused a placebo -corrected decrease in body weight (upto -3.4 kg) systolic BP (uptill -3.9 mm Hg), diastolic BP (uptill -2.3 mm Hg), and in total comparable outcomes with 10 mg and 25 mg across studies following 26 weeks. In EASE-3, low dose Empagliflozin 2, 5 mg had the similar good trend but to lower amount act 2 higher dosages; weight decrease (-1.8 kg) and lower systolic BP (-2.1 mm Hg).

3.3 Difference from other SGLT2 Inhibitors

Encouraging outcome were shown by canagliflozin both 100 mg and 300 mg in combination with insulin vis-a-vis placebo in combination with insulin, demonstrating decreases in insulin dosages, Hb A1C as well as body weight. The group of Peters, Henry demonstrated that 36.9%, 41.4% and 14.5% of subjects achieved the initial aim (i.e. over 0.4% decrease of Hb A1C without an increase in weight regarding canagliflozin 100 mg, canagliflozin 300 mg, and placebo respectively [18].

Tandem program with respect to sotagliflozin i.e., a double SGLT1/2 Inhibitor showed enough clinical effectiveness , having an average decrease in Hb A1C in contrast to placebo of -0.46%, along with weight loss of -3kg in subjects having therapy utilizing 400 mg sotagliflozin vis-a-vis placebo for a duration of 24 weeks (in case of Tandem 3 study) [19]. Both Tandem 1 and 2 validated the results carried out in USA/Canada along with Europe for 52 weeks. Noticeably, sotagliflozin enhanced the time in range for >3hrs. without enhancing the time in hyperglycemia [20,21].

Similarly DEPICT program was conducted with respect to dapagliflozin in case of T1DM. 2 studies (DEPICT 1 and 2) gave similar outcomes. Though, there was similarity in the designs of both studies, few changes observed were between these 2 studies implying variations in the geographic scattering of the pts. i.e. >number of Asians along with lesser visits in the case of DEPICT 2. As far as DEPICT 1 study was concerned, badly controlled T1DM patients with regards to their DM status was concerned were supposed to randomly receive once/day dapagliflozin 5 mg, dapagliflozin10 mg or placebo.

Following 24 weeks of treatment dapagliflozin decreased Hb A1C -0.42% and -0.45% utilizing 5 mg and 10 mg dosage respectively, in contrast to placebo of -0.03%. Similarly in contrast to placebo, those subjects having therapy utilizing dapagliflozin 5 mg, dapagliflozin10mg lost -2.96 kg and-3.7 2kg [13]. In the same way DEPICT 2 study revealed same outcomes i) Average alteration in Hb A1C as compared to placebo, was -0.37% and -0.42%, with dapagliflozin 5 mg, and 10 mg respectively.

Similarly in contrast to placebo, those subjects having therapy utilizing dapagliflozin 5 mg, and 10 mg lost -3.2 kg and-3.7 kg [22]. These changes in Hb A1C, weight as well as decrease in insulin dosage was mostly sustained till 52 weeks [13]. Further for the DEPICT program, this dapagliflozin escalated the time in range, without enhancing the time in hyperglycemia, that is a property that has lot of significance for T1DM patients.

4. Safety as well as Empagliflozin Tolerance in T1D

4.1 Hypoglycemia

In view of independent mode of action by themselves SGLT 2 Inhibitors don't effect hypoglycemia on their own. Yet giving SGLT 2 Inhibitors with insulin has the potential nature of enhancing the chance of hypoglycemia. An equivalent total chance of symptomatic hypoglycemia was demonstrated by Rosentock et al. [17] regarding Empagliflozin 10 as well as 25 mg vis-a-vis placebo, till 52 weeks [17]. Similar pattern was demonstrated by Empagliflozin 2.5 mg till 26 weeks. Further no enhancement of severe hypoglycemia was reported -1.2%, 4.1% and 2.7% and 3.1% for Empagliflozin 2.5 mg, 10 as well as 25 mg vis-a-vis placebo. These outcomes are similar to what was seen with the SGLT 2 inhibitors programs.

4.2 Infections of the Urogenital System

Greater incidence of Urogenital Infections with SGLT 2 Inhibitors would be anticipated in view of urinary glucose effecting extra growth of commensal microorganisms residing in the Urogenital System. With the T2DM studies it was shown that actually the chance of genital Infections, but not that of urinary Infections was escalated by this group of drugs. Similarly in the EASE studies conducted with Empagliflozin in T1DM, genital Infections presented more with Empagliflozin as compared to placebo. In cases of Empagliflozin 10 mg and 25 mg 12.8% and 14.3% of subjects documented genital Infections vis-a-vis just 4.3% of placebo subjects. In case of EASE 3, subjects on Empagliflozin 2.5 mg had double chance of acquiring genital Infections as compared to placebo. But still the Infections seen were usually mild to moderate getting treated simply with the use of standard treatment. Conversely, UTI took place with same chance. These results are again similar to those found with other SGLT 2 Inhibitors [17].

4.3 Diabetic ketoacidosis (DKA)

Utilization of SGLT 2 Inhibitors reduces blood glucose amounts in a non- insulin dependent basis. Thus insulin dosage can be decreased usually. In maximum number of T1DM subjects adding SGLT 2 Inhibitors causes a reduction in insulin dosage, to prevent hypoglycemia. But when insulin is decreased very rapidly, a key amount might occur when insulin amounts are not that raised to be able to repress lipolysis in peripheral fat tissues, resulting in ketone body development and ultimately causing DKA. Whatever programs have been evaluated with respect to SGLT 2 Inhibitors or SGLT1/2 Inhibitor s in T1DM have considered this chance, giving training to both the medical teams as well as patients to check the ketone body levels and have taught them regarding the way to prevent development of DKA. Despite that, all programs documented an imbalance in the occurrence of DKA changes, with 2-4 more DKA changes documented in SGLT 2 Inhibitors therapy subjects. Moreover in the EASE program, the incidence of validated DKA on Empagliflozin 10 mg and 25 mg dosage was > than placebo, respectively 4.3%, 3.3% and 1.2% (pooled outcomes of EASE 2 and 3). Severity of DKA was dosage based. In the Empagliflozin 25 mg, one patient died. DKA was more prevalent in female patients and in those patients who were on insulin pumps, all DKA patients were induced by a precipitating factor like illness or material failing. What was noted was that there was no escalation of DKA by 26 weeks in the Empagliflozin 2.5 mg as compared to placebo (0.8% versus 1.2%) [17].

4.4 Other systems

Hepatic systems, acute kidney problems or bone fractures rate was similar in all groups of Empagliflozin as compared to placebo [17].

5. DISCUSSION

For the individuals affected by T1DM there is a requirement to help decrease insulin dosages. Despite improvement of quality of life (QOL) of people having

T1DM, problems like hypoglycemia, enhancement of weight and differences in glucose profiles are a challenge. Empagliflozin and SGLT 2 Inhibitors, broadly are efficient glucose reducing agents, which are also effective in T1DM. A clear improvement in Hb A1C, body weight , glucose differences along with reduction of daily insulin dosage the phase II and III studies recently done that had EASE as part for Empagliflozin, was displayed. But till date utilization of Empagliflozin is not done in T1DM.

EASE program special feature was that in this case a very low of the drug was used , with little but still existing , changes on the metabolic effects , but what was noticed is a <chance of DKA. On exploring deeply towards the DKA chances in the greater dosages of Empagliflozin and thus extending to that seen with dapagliflozin, canagliflozin and Sotagliflozin, it is apparent that total chance of DKA was little. On comparison of the DKA chances in the SGLT 2 Inhibitors studies in placebo therapy patients, the risk was lesser than that seen in the real world. This gives proper evidence that deeply educating along with how to rescue the patients regarding what needs to be utilized on presence of ketones might prevent DKA in many instances. Anyhow imbalance still persists. The point that gives tension is that DKA in T1DM individuals on SGLT 2 Inhibitors is that the glycemic amounts are not so escalated since both clinicians awe patients are accustomed to if not using SGLT 2 Inhibitors associated with glycosuria. Glycemic amounts in DKA patients in SGLT 2 Inhibitors therapy subjects are usually <250 mg/DL, threshold utilized by the American Diabetes Association in defining DKA, and hence known as "euglycemic DKA." Danger is there when patients land up with unexperienced medical personnel. What transpired in the DKA event in that individual who expired in the Empagliflozin 25 mg arm will give us >insight regarding the most risky cases but already what is evident is that those T1DM individuals who are on insulin pumps were the ones who progressed till overt DKA. Further many times, an incidence that precipitated it like infection /omitting insulin dosage was there. With the most unusual thing in EASE program, where a very low dosage (2.5 mg) of the drug was used, that was below the total potential of Empagliflozin in glycosuria stimulation. This particular arm did not show any imbalance in DKA was seen vis a vis placebo, that shows large chance of hitting on a "sweet spot" that can be utilized for prescribing these drugs. Although lot of restraint should be utilized as far as too much enthusiasm is used since this was only one study having a 26 week time point of evaluation. In the beginning of DEPICT program same type of findings were seen in which a 24 week evaluation of the DEPICT 1 study also demonstrated no imbalance of DKA [23], with an imbalance observed kin the DEPICT 2 study and also showing up in DEPICT 1 study at 52 weeks [22]. Anyhow, when thinking of utilizing SGLT 2 Inhibitors in T1DM individuals, it needs to be done in very properly selected subjects. Such subjects need to be properly taught regarded the chances of not taking adequate insulin or material failure and detailed regarding the DKA symptomatology like nausea, vomiting as well as abdominal pain and hence taught to check ketone bodies if not having a healthy feel, despite normal glucose amounts since DKA can present at much lesser glucose amounts and to consult her physician in case ketones are positive [24]. Moreover, physicians need to decrease insulin therapy cautiously i.e. not >20% and shut the supplementation of SGLT 2 Inhibitors on the T1DM individuals feeling ill or needs to undertake surgery. Also not all T1DM individuals are suitable for adjuvant treatment. Those having an enhanced Hb A1C levels suggest that already they are getting much lesser insulin dosage and not get any therapy which will decrease insulin dosages further.

As already reviewed by us earlier regarding SGLT 2 Inhibitors, with special highlighting of Empagliflozin in T1DM individuals is on the basis of CVOTs and renal beneficial effects seen with Empagliflozin in T2DM subjects. Similarly T1DM individuals have a

>predisposition to a higher CVS and renal worsening. Empa-reg outcome trial displayed a definite improvement in CVD and installing the progress of renal problems in T2DM subjects having prior CVD. Later programs like CANVAS, DECLARE for canaglifozin, and dapaglifozin respectively verified this and further increasing the scope of good CVS effects, especially to heart failure as well as renal conferring protective effects despite no CVD [8-12]. Till now not clear similar benefits will get conferred in T1DM individuals, but many pointers that it is true. CVS good effects is due to lot of benefits of SGLT 2 Inhibitors, occurring at similar time like lower BP, increased dieresis along with decreased pre and afterload, weight loss and enhanced haematocrit. A posit introduced recently points that the small escalation of ketones amount might give a more efficient energy substrate to the heart [25].

Empagliflozin has demonstrated a reduction in intraglomerular pressure for increasing the hyperfiltration in T1DM individuals [26]. Cherney et al. [26], gave T1DM individuals. 25 mg for 8weeks to those with and without hyperfiltration, GFR was markedly decreased by 33 ml/min/1.73 m^2, pointing that what had been observed in T2DM subjects on renal benefits might also occur in T1DM individuals. Of note, the study which concentrated on renal endpoints, EMPA-KIDNEY [27], will be the lone study utilizing SGLT 2 inhibitors, in T1DM individuals.

6. CONCLUSIONS

There is enhanced proof developing on the probability of Empagliflozin, like rest of SGLT 2 inhibitors in T1DM subjects. But clinicians , subjects as well as regulators will need to balance the probable short time and long time advantages of these adjuvant treatments in T1DM subjects versus the probable acute adverse effects, especially in the little but actual chance of DKA.

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