DOI: https://doi.org/10.53350/pjmhs20221611537

ORIGINAL ARTICLE

Evaluation of Dapagliflozin's Impact in Type 2 Diabetes Management as A Supplement to Metformin

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ABSTRACT

Objective: to analyzing the efficacy and safety of dapagliflozin in type 2 diabetics already taking metformin.
Methodology: In this observational study at Madinah Teaching Hospital Faisalabad during July 2021 to October 2022, we enrolled 100 cases of either gender with 40-70 yrs, the impact of dapagliflozin 10 mg once daily in diabetics already taking metformin 1.5-2.5 g/day (DAPA + MET), and who had a follow-up visit at 6 months. The effectiveness was measured by the change in HbA1c at baseline at 12 months, as well as the change in BMI, creatinine and microalbumin levels at 6 months.
Results: The effect and safety of Dapagliflozin was evaluated in terms of BMI before treatment 11.52+5.87 which reduced to 27.11+8.63 with significant difference, HbA1c(%) before treatment was 8.78+0.68 which reduced to 7.26+0.85 with a significant difference, sCr(µmol/L) was also reduced from baseline 147.76+6.92 to 142.76+6.41, Microalbumin(µg/mg) was 126.60+4.90 before treatment and 124.48+7.42 after treatment, showing a significant reduction.
Conclusion: Patients with type 2 diabetes who received dapaglifozin as an add-on medication is found with a significant reduction in their HbA1c level as well as their FBG during a 6-month treatment period.
Keywords: Type 2 diabetes

INTRODUCTION

Insulin insufficiency or reduced insulin activity leads to diabetes mellitus(DM), a metabolic condition that causes a variety of health problems. Obesity considered as an independent risk factor responsible for type 2 diabetes mellitus, and linked insulin resistance in peripheral tissues.[1-2] Type 2 diabetes patients who are also obese have a much higher chance of developing renal failure and cardiovascular disease. The concentration of lipids in adipocyte cytoplasm has been shown to change, and this has been linked to the onset of insulin resistance. Furthermore, peripheral insulin resistance or decreased insulin action may occur as a result of altered adipokine secretion.[2]

The recent data evaluated by IDF, indicated that the DM is prevalent around 12.8% in middle east population, and it is anticipated that this number would rise to 14.2% by the year 2030.[3] In the Middle East, obesity in men is reported as 24% lower than females i.e. 40%, while the incidence of obesity is 48% among males and 35% among girls. The percentage of people who are overweight is higher among males.[4] The rising rates of higher BMI in type 2 diabetes provide a serious challenge for the administration of public health policy.[5]

It is recommended that metformin be administered as the first intervention for individuals with T2DM, for the pharmacological therapy of diabetes. Patients on metformin should have their vitamin B12 levels monitored regularly,[6-7] since this deficit is a common adverse effect of the drug. Patients with renal illness, liver damage, or other CVS problems that lead to low levels of oxygen in the blood are particularly vulnerable to lactic acidosis from metformin.[8] The recommendations advocate supplementing hypoglycemic medications with sodium-glucose cotransporter 2 (SGTL2) inhibitors and/or glucagon-like peptide 1 receptor agonists for type 2 diabetics with cardiovascular or CKD.[7] Because of their versatility, SGTL2 inhibitors may be used in tandem with other families of hypoglycemic drugs.[9] If administered together, the drugs would enhance the patient's health, reverse the pathology, and prevent any further issues from developing as a result of the current treatment plan. Drug combinations for type 2 diabetes should be able to enhance the patient's metabolic state in addition to lowering glycosylated haemoglobin levels (HbA1C). [9]

Although it has been recommended that combining SGTL2 inhibitors with metformin might help reduce hyperglycemia that is resistant to metformin alone,[9] the safety concerns around these drugs have yet to be addressed. High glycosuria produced by SGTL2 inhibitors has not yet been well addressed as a cause of genital infections. Further, hypotension might develop if the body loses too much water due to SGTL2 inhibitor-induced osmotic diuresis.[10] Concerns about the use of SGTL2 inhibitors in diabetes have been highlighted on several occasions owing to their significant role in triggering diabetic ketoacidosis.[11] Canagliflozin, an SGTL2 inhibitor, was linked to pancreatitis in type 2 diabetes patients in two studies published in 2015.[12-13] When used in conjunction with first-line hypoglycemics, GLP-1 agonists are among the most effective classes of adjuvant hypoglycemic medications.[14] Pancreatitis is a key cause for alarm when it comes to GLP-1 agonist usage,[14-15] along with other GI problems (nausea, vomiting, and constipation) and infections, as well as acute renal damage. Acute pancreatitis has been documented in patients using liraglutide and exenatide.[16-17] In addition, there have been several reports linking incretin-based medicines to pancreatitis and pancreatic cancer, which has led to worries about their long-term use.[18] Incretin-based medications have been linked to an increased risk of developing pancreatic and thyroid cancer, according to studies using data from the FDA's Adverse Events Reporting System.[19-20] As with bone cancer, there is a correlation between exenatide usage and an increased risk of bone fractures.[21]

One of the most common microvascular complications of diabetes is diabetic nephropathy (DN), which is characterised by albuminuria and a reduction in glomerular filtration rate (GFR).[22] Hyperglycemia and glucose metabolites such advanced glycation end products are believed to be the root cause of the loss of podocytes, hyperfiltration of endothelial cells, expansion of mesangial cells, and thickening of the glomerular basement membrane (AGEs).[23] In spite of medical progress, many individuals living with DN continue to deal with incapacitating symptoms that make even the simplest of tasks a challenge or an impossibility.[24] Thus, the treatment of DN has to include more cutting-edge therapeutic techniques.

The probability of renal disease progression was lowered by 45% when sodium-glucose cotransporter-2 inhibitors (SGLT2i) were used.[25] By increasing urine glucose excretion, body weight, systolic blood pressure, and albuminuria, the SGLT2i dapagliflozin has been found to reduce glycated haemoglobin (HbA1c).[26] Patients with type 2 diabetes who took dapagliflozin had considerably lower odds of heart failure and worsening chronic kidney disease, according to results from a major cardiovascular outcome study.[27] Recently, dapagliflozin's potential as a treatment for DN has been the subject of some research. Combining ticagrelor with dapagliflozin has been shown to have synergistic

benefits in reducing diabetic nephropathy in mice with type-2 diabetes mellitus.[28] Dapagliflozin therapy also showed dose-dependent improvements in histological examination, apoptotic and inflammatory markers compared to diabetes vehicles, indicating that the drug may have renoprotective benefits, i.e. encouraging in diabetics with nephropathy. [29]

Additionally, in rats with fructose-streptozotocin-induced diabetes, dapagliflozin reduces early indicators of diabetic nephropathy.[30] However, the majority of studies on dapagliflozin's therapeutic impact for DN have been conducted in mice or rats, and clinical data are few.

The purpose of this research was to examine the effectiveness and safety of dapagliflozin in patients suffering from type 2 diabetes who were simultaneously taking metformin in clinical practice in Pakistan.

METHODOLOGY

In this observational study at Madinah teaching hospital Faisalabad, we enrolled 100 cases of either gender with 40-70 yrs, the efficacy and renal safety was evaluated for dapagliflozin 10 mg in a day in type 2 diabetics who were also taking metformin 1.5-2.5 g/day (DAPA + MET), and who had a follow-up visit at 6 months. Further, these cases were unable to adequately control of diabetes, never discontinued therapy, never experienced any side effects, had normal renal function (eGFR rate >60 mL/min), changed their eating habits in accordance with our recommendations, and since baseline, had undergone all blood tests in our outpatient clinic laboratory. The exclusion criteria was if they could not self-test their blood sugar at home or if they could not make changes in accordance with our recommendations. Age, sex, waist size, weight, systolic and diastolic blood pressure, and illness duration were all included as baseline data. According to customary clinical procedure and the clinician's judgement, insulin or glimepiride were added to the treatment plan at the same time as dapagliflozin was started in patients whose HbA1c level was less than 7.5% (DAPA + MET + other glucose-lowering medications). The effectiveness was measured by the change in HbA1c from baseline at 6 and 12 months, as well as the change in BMI, creatinine and micralbumin levels at 6 months. The haemoglobin A1c levels were checked at home, and doctor's visits were scheduled at three months or as required.

RESULTS

In our study, 56.19+9.63 years was meanage, BMI was 29.28+1.49, duration of diabetes was 11.52+5.87 years, male cases were 54(54%) whereas female candidates were 46(46%).

The effect and safety of Dapagliflozin was evaluated in terms of BMI before treatment 11.52+5.87 which reduced to 27.11+8.63 with significant difference, HbA1c(%) before treatment was 8.78+0.68 which reduced to 7.26+0.85 with a significant difference, sCr(µmol/L) was also reduced from baseline 147.76+6.92 to 142.76+6.41, Microalbumin(µg/mg) was 126.60+4.90 before treatment and 124.48+7.42 after treatment, showing a significant reduction.

Table 1: General characteristics of the patients

Age(years)	56.19+9.63
BMI	29.28+1.49
Duration of disease	11.52+5.87
Male(%)	54(54%)
Female(%)	46(46%)

Table 1: Comparison efficacy and safety of Dapagliflozin

	Before treatment	6 months After treatment	P value
BMI	29.28+1.49	27.11+8.63	0.0001
HbA1c(%)	8.78+0.68	7.26+0.85	0.0001
sCr(µmol/L)	147.76+6.92	142.76+6.41	0.0005
Microalbumin(µg/mg)	126.60+4.90	124.48+7.42	0.04

DISCUSSION

Lifestyle modification methods and/or metformin are often used as first treatments for type 2 diabetes. When insulin resistance is present, -cell function decreases, making it difficult to maintain glycemic control and often requiring additional therapy. Since metformin enhances insulin sensitivity it may be helpful to supplement it with treatment that operates through an insulin-independent mechanism. An innovative method to lower hyperglycemia that does not rely on insulin production or action is to inhibit sodium-glucose cotransporter 2 (SGLT2). The kidney's proximal tubule contains an enzyme called sodium-glucose cotransporter 2 (SGLT2), and blocking it might lead to novel treatments for type 2 diabetes. When administered alone, or in combination with metformin, sulfonylureas, thiazolidinedione, or insulin, dapagliflozin, a strong and selective SGLT2 inhibitor, improves glycemic control in individuals with type 2 diabetes.

Clifford J Bailey and colleagues,[31] in a study revealed that five hundred forty-six people were assigned at random to one of four different treatments. Placebo participants were less likely to finish the 78-week double-blind extension period (63.5% vs. 68.3% to 79.8%, respectively) than those in the dapagliflozin groups. The average decrease in HbA1c from baseline (8.06%) at week 102 was +0.02% for placebo, -0.48% (P = 0.0008), -0.58% (P 0.0001), and -0.78% (P 0.0001) for dapagliflozin 2.5 to 5 mg, and -0.78% (P 0.0001) for dapagliflozin 10 mg. Moreover, after 102 weeks, patients in all dapagliflozin groups had maintained decreases from baseline in FPG (-1.07 to -1.47 mmol/l) and body weight (-1.10 to -1.74 kg), whereas patients in the placebo group had increases in both outcomes. hypoglycemic episodes occurred seldom and were mild. One patient on dapagliflozin and one on placebo discontinued treatment because of symptoms suggesting a vaginal infection (dapagliflozin 5 mg). One patient stopped using dapagliflozin because of symptoms suggesting a urinary tract infection, but no such patient stopped taking the placebo (dapagliflozin 2.5 mg). It was concluded that the addition of dapagliflozin to metformin for 102 weeks resulted in persistent reductions in HbA1c, fasting plasma glucose, and weight in individuals with type 2 diabetes who were poorly managed on metformin alone. This was accomplished without an increase in the risk of hypoglycemia. This study validates our results regarding efficacy and safety of the add-on therapy.

Our findings were corroborated by a more recent research which shown that Dapagliflozin, when administered in conjunction with other OHAs or insulin, successfully lowered HbA1c level and FBG within 6-12 months.[32]

Multiple analyses of SGLT2 inhibitors have shown dapagliflozin to be effective. Studies[33-34] showed its efficacy as monotherapy for newly diagnosed T2-DM patients. Additionally, it has been shown to be efficacious when used in conjunction with other oral hypoglycemic medications in various research groups.[35-36] In addition, studies demonstrated the same degree of effectiveness when dapagliflozin was administered in combination with insulin, with the added advantage of reducing insulin demand.[37-38] The effectiveness of dapagliflozin has been shown across a variety of groups, but mostly in the Western world. As an adjunct to insulin, with or without oral antidiabetic medications (OADs), Yang et al. discovered that dapagliflozin dramatically improved glycemic control[39] in patients from Asia. However, there has been a dearth of research on the efficacy of these medicines in a Middle Eastern population, which presents a unique set of challenges due to differences in genetics,[40-41] as well as in demographics, culture, and way of life.[42-43] All of these factors have the potential to affect how well an individual responds to SGLT2 inhibitors, particularly dapagliflozin.

CONCLUSION

Patients with type 2 diabetes who received dapaglifozin as an add-on medication is found with a significant reduction in their HbA1c level as well as their FBG during 6-month treatment period.

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