SHORT REPORT

The synergy of linagliptin and empagliflozin in catering to diabetes mellitus in Pakistan

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Abstract

Diabetes is rapidly increasing globally, especially in low- and middle-income countries, with Pakistan ranking third in prevalence, having 33 million people. The lack of adherence to the first-line treatment, metformin, mainly due to gastrointestinal side effects, is a significant concern. A novel approach for managing type 2 diabetes in Pakistan is to combine linagliptin and empagliflozin. Linagliptin is well-tolerated and suitable for those who cannot tolerate metformin, while empagliflozin reduces cardiovascular risks and nephropathy, showing promising results in controlling diabetes with minimal side effects. The synergy between linagliptin and empagliflozin could greatly improve diabetes management and patient wellbeing. It is recommended that healthcare providers in Pakistan use social media and seminars to educate the public on this new treatment option to tackle the diabetes crisis effectively.

Key Words: Diabetes, Linagliptin, Empagliflozin, Combination therapy, Pakistan.

DOI: https://doi.org/10.47391/JPMA.11145

Introduction

Diabetes, primarily type 2 diabetes mellitus (t2DM), has seen a significant global rise in the past 30 years, with about 422 million people affected, causing 1.5 million deaths annually.[1] Roughly 80% of the global population of adults with diabetes, estimated at 463 million individuals, resides in low- and middle-income countries (LMICs).[2] In 2019, 37.3 million Americans, 11.3% of the population, had diabetes, with 28.7 million diagnosed and 8.5 million undiagnosed cases. Additionally, 1.4 million new diabetes cases are diagnosed annually, while 96 million adults aged 18 years and older have prediabetes.[3]

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Submission complete: 27-11-2023 **First Revision received:** 16-04-2024
Acceptance: 28-09-2024 **Last Revision received:** 27-09-2024

Diabetes not only affects the older adult population, but can affect the younger population as well, as statistics showed that approximately 283,000 Americans aged <20 years have been diagnosed with diabetes, comprising 0.35% of this age group. In 2014-15, there were 18,200 new cases of type 1 diabetes mellitus (T1DM) and 5,800 new cases of T2DM in younger population.[3] Diabetes has caused over 100,000 annual deaths in the United States for the past two years, prompting a national commission to advocate for a comprehensive approach from the federal government to combat this growing crisis.[4] In 2021, Pakistan had a total adult population of 123.5 million, with a diabetes prevalence of 26.7% among adults, resulting in approximately 32.96 million cases in the country.[5]

The current short report was planned to draw on a combination of personal clinical experiences and a comprehensive review of existing literature regarding the use of a linagliptin and empagliflozin in combination for the management of diabetes mellitus in Pakistan.

Methods and Results

The perspective regarding the combination of linagliptin and empagliflozin, based on experience, indicates that most patients encountered in the outpatient department (OPD) exhibit non-compliance with metformin due to its side effects, with gastric irritation being the most commonly reported complaint. The study, conducted at Aga Khan University Hospital, Karachi, Pakistan, from the start of August 2023 to mid-October 2023, observed that this non-compliance with metformin posed additional risks for diabetes patients, as it could further exacerbate complications related to the disease. A 2016 interventional study in Isfahan, Iran, reported that 75 T2DM patients switched from metformin tablets to metformin capsules. The transition significantly reduced gastrointestinal (GI) side effects, dropping the prevalence from 53.3% to 21.3%. Additionally, glycated haemoglobin (HbA1c) levels improved, and patient satisfaction was high, suggesting that switching to metformin capsules could effectively mitigate GI side effects without introducing new complications.[6]

However, Pakistan still has a larger population affected by

T2DM. Therefore, we should have more options to cover the whole diabetic population better and ensure medication compliance. The next option is linagliptin, which effectively treats T2DM. According to guidelines from the American Diabetes Association and the European Association for the Study of Diabetes, linagliptin and other therapies based on incretions are recommended as second-line treatment options, following metformin, the first-line choice.[7]

When metformin is either contraindicated or does not provide adequate therapeutic benefits, it is expected to employ a combination of different therapeutic agents to manage T2DM effectively. Linagliptin is a new dipeptidyl peptidase 4 (DPP-4) inhibitor for treating T2DM. The drug received approval from the Federal Drug Administration (FDA) in 2011.[8] One can be prescribed linagliptin to avoid the side effects of metformin. However, these agents may also be considered initial treatments for individuals who cannot tolerate metformin. Linagliptin, like other incretion-based therapies, is a versatile medication. It enhances insulin secretion, lowers glucagon production, delays stomach emptying, fosters a feeling of fullness, and reduces appetite.[9] Its benefits encompass minimal risk of severe hypoglycaemia, weight neutrality, and generally well-tolerated side effects.

Linagliptin is an approved oral antidiabetic drug, inhibiting DPP-4. What sets linagliptin apart from other DPP-4 inhibitors is its primary excretion through the enterohepatic system, allowing it to be used without requiring dosage adjustments in patients with chronic kidney disease (CKD).[10] Additionally, a 2017 study in Turkey focussed on insulin-dependent T2DM patients with CKD, and found that adding linagliptin to their treatment regimen led to improved renal function, as indicated by an increase in estimated glomerular filtration rate (eGFR), without significant changes in proteinuria or glucose control. This suggests that linagliptin may offer a promising therapeutic avenue for managing diabetic nephropathy and slowing CKD progression in this patient population.[11]

Linagliptin is a very new drug in Pakistan, and many people are unaware of its benefits in treating T2DM. This drug can help treat such patients and could increase the compliance level. Healthcare providers should arrange social media seminars to spread the news related to this medication to control the prevalence of T2DM in Pakistan.

Yet another essential antidiabetic drug is Empagliflozin. It is a medication used to treat T2DM that inhibits sodium-glucose co-transporter-2 (SGLT-2) found in the proximal tubules in the kidneys. The drug, approved in 2014 by the FDA, can be used as a single regime, or in combination with metformin and linagliptin while targeting a reduction of cardiovascular risks and nephropathy.[12] The combination of various DDP-4 and SGLT-2 inhibitors has shown significant improvement in diabetes control regarding fasting blood sugar (FBS), random blood sugar (RBS), and HbA1c reductions, and their complications, including stroke and myocardial infarction (MI).[13]

Clinical observations indicate significant benefits from using a combination of oral hypoglycaemic agents and insulin therapy for patients with poorly controlled diabetes. This approach substantially reduced HbA1c levels and helped prevent complications, such as stroke, MI, retinopathy, nephropathy and neuropathy. Patients previously on 4 daily insulin injections found this combination therapy more convenient and cost-effective, reducing the burden and embarrassment associated with frequent injections. Furthermore, these oral agents are weight-neutral or even promote weight-loss, in contrast to insulin's known side effect of weight-gain. Over time, some patients could transition to monotherapy with oral hypoglycaemic agents (OHAs) due to improved glycaemic control. Some even reported achieving HbA1c levels within non-diabetic ranges when combining these agents with diet control and regular exercise. This suggests the potential for reversing T2DM through a comprehensive approach involving OHAs, diet, exercise and weight management. Further studies may provide insight into the feasibility of diabetes reversal.

Besides, the literature also supports that the combination therapy of empagliflozin and linagliptin significantly reduces genital infections. It is also well-tolerated with no adverse ketosis acidosis events, and has high efficacy in lowering HbA1c levels.[14]

Conclusion

The global trend of diabetes, particularly in LMICs, like Pakistan, is on the rise, necessitating effective and well-tolerated treatment options. The efficacy of linagliptin, a DPP-4 inhibitor, and empagliflozin, an SGLT-2 inhibitor, offers a promising alternative for T2DM management, especially for patients who experience non-compliance with metformin due to side effects. However, increased awareness and education on this medication's benefits are crucial in Pakistan to control the growing prevalence of T2DM and to improve patient compliance.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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AUTHORS' CONTRIBUTIONS:

AA: Concept, design, revision, drafting, final approval and agreement to be accountable for all aspects of the work.

KK, MS: Design, drafting, final approval and agreement to be accountable for all aspects of the work.