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Comparing Effect of Sitagliptin versus Empagliflozin as Add on Therapy to Metformin in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) presents a substantial health challenge. Metformin is established as a standard treatment. This study evaluates sitagliptin, a dipeptidyl peptidase-4 inhibitor, and empagliflozin, a sodium-glucose cotransporter-2 inhibitor, as adjunct therapies to improve T2DM management. **Objective:** To compare effect of sitagliptin versus empagliflozin as add on therapy to metformin in patients with T2DM. **Study Design:** It was a prospective comparative study. **Settings:** This study was conducted at the Department of Medicine, DHQ Teaching Hospital, KMU Institute of Medical Sciences, Kohat Pakistan. **Duration:** 6 months period from March-September, 2023. **Methods:** A sample size of 100 cases was randomly assigned to either Group A or Group B. In conjunction with the standard metformin regimen (1000 mg twice daily), eligible patients were randomly assigned in a 1:1 ratio to receive either 50 mg of sitagliptin (Group A) or 12.5 mg of empagliflozin (group B) twice daily over 12 weeks. Study visits were scheduled at screening, weeks 0, and 12 of therapy, with no permitted dosage adjustments for the investigational drug. All the data was collected in a predesigned format and data analysis was done using SPSS 27.0. **Results:** Mean age of the patients in this study was 52.58±10.0 years in which 43.0% (n=43) participants were male while remaining 57% (n=57) were females. Both the groups were comparable with each other and did not possess any inherit difference between them with regard to all baseline characteristics (p-value >0.05. After three months mean HbA1C in group B was significantly less than group A (8.00±0.13 vs. 7.42±0.08%; p-value=0.000). Mean change in HbA1c at three months from the values at presentation was significantly high in group B than group A (-0.70±0.25 vs. -1.33±0.17%; p-value=0.000). Comparison of mean weight between the groups shows significantly less mean weight in group B at three months than group A (64.14±4.25 vs. 61.84±4.89 kg; p-value=0.014). Mean change in weight at three months was significantly high in group B than group A. When mean change in HbA1C and mean reduction in weight in both the groups was stratified for age and gender, it produced same significance for all the stratifications (p-value=0.000). **Conclusion:** In conclusion, our study reveals that empagliflozin leads to superior glycemic control and greater weight reduction compared to sitagliptin as add on therapy to metformin in patients T2DM. These findings emphasize the potential benefits of individualized treatment strategies for optimized outcomes in T2DM management.

Keywords: *Empagliflozin, Metformin, Sitagliptin, Type 2 Diabetes Mellitus.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) stands as a formidable global health challenge, a condition intricately woven into the fabric of both genetic predisposition and environmental triggers.[1] This metabolic disorder manifests through the complex interplay of insulin resistance and impaired insulin secretion, resulting in elevated blood glucose levels and far-reaching effects on overall health.[2]

Beyond the immediate symptoms lie the profound repercussions of T2DM, leaving an indelible mark on global health. The stark reality is evident in the sobering statistics from 2019, where diabetes claimed the lives of a staggering 4.2 million individuals worldwide.

Simultaneously, an alarming 463 million adults aged 20-79 grappled with the intricate daily management of T2DM, placing an unprecedented burden on healthcare systems globally. This escalating prevalence underscores the pressing need for a comprehensive understanding of the multifaceted nature of this chronic condition.[3]

Within this global panorama, Pakistan emerges as a poignant focal point in the narrative of T2DM prevalence.[4] Reports reveal a substantial prevalence rate of 16.96%, emphasizing the urgent necessity for effective management strategies that are uniquely tailored to the challenges faced by the Pakistani population.[5]

In the expansive landscape of T2DM management, metformin has long stood as a cornerstone therapy. However, the evolving understanding of this metabolic disorder prompts a nuanced exploration of alternative treatment modalities.[6,7] In this context, sitagliptin and empagliflozin have garnered attention not only for their distinct mechanisms of action in modulating glucose metabolism but also for the nuanced controversies that surround their use.[8]

The intrigue surrounding sitagliptin and empagliflozin deepens as we delve into the realm of glycemic control. Mubashir *et al*. (2022)[9] contribute to the discourse by elucidating a statistically significant mean reduction in HbA1c from baseline of -0.81 ± 0.19% for Sitagliptin and -1.13 ± 0.24% for Empagliflozin. However, the narrative takes an intriguing turn with Khan *et al*.'s (2022)[10] findings, where the mean change in HbA1c (-0.82%±1.57 for vildagliptin and -0.97%±0.68 for empagliflozin) yields statistically insignificant results with a p-value of 0.980.

The diversity of outcomes in these studies underscores the critical importance of contextual factors influencing the efficacy of sitagliptin and empagliflozin. As we navigate these intricacies, the imperative remains to elucidate a path forward in the management of T2DM that is not only effective but also tailored to the diverse needs and nuances of the global population. This exploration necessitates a continued dialogue and a nuanced approach to balance the potential benefits and controversies surrounding these pharmacological agents, thereby paving the way for a more personalized and effective T2DM management strategy.

METHODS

This prospective comparative study was conducted at the Department of Medicine, DHQ Teaching Hospital, KMU Institute of Medical Sciences, Kohat. A sample size of 100 cases, with 50 in each group, was determined based on an 80% power of the test, a 5% level of significance, and expected mean change in HbA1c to be -0.81 ± 0.19% for Sitagliptin and -1.13 ± 0.24% for empagliflozin.[9] Inclusion criteria was patients of both the genders with T2DM (HbA1c > 7%). Patients with HbA1c>10%, aspartate aminotransferase, elevated alanine aminotransferase, pregnancy, INR>1-2, creatine phosphokinase, high bilirubin, albumin < 3.5g/dl, pancreatitis, urinary tract infection, chronic liver disease, renal impairment (Crcl ≤ 50 ml/min), and diabetic ketoacidosis were excluded. Following the acquisition of informed written consent, patients were randomly assigned to either Group A or Group B. In conjunction with the standard metformin regimen (1000 mg twice daily), eligible patients were randomly assigned in a 1:1 ratio to receive either 50 mg of sitagliptin (Group A) or 12.5 mg of empagliflozin (group B) twice daily over 12 weeks. Study visits were scheduled at screening, weeks 0, and 12 of therapy, with no permitted dosage adjustments for the investigational drug. All the data was collected in a predesigned format and data analysis was done using SPSS 27.0.

RESULTS

Mean age of the patients in this study was 52.58±10.0 years in the range of 35-70 years in which 43.0% (n=43) participants were male while remaining 57% (n=57) were females. Mean weight of the patients at presentation was 68.36±4.56 kg whereas as mean HbA1c (%) was 8.72±0.19. Data is given in Table 1.

Table 1: Baseline characteristics of study sample

Characteristics		Participants (n=100)
Age in Years	35-70	52.58±10.00
	35-50 years	44 (44.0%)
	51-70 years	56 (56.0%)
Gender	Male	43 (43.0%)
	Female	57 (57.0%)
Weight (kg)		68.36 ± 4.56
HbA1c (%)		8.72 ± 0.19

Both the groups were comparable with each other and did not possess any inherit difference between them with regard to all baseline characteristics (p-value >0.05), as given in Table 2.

Table 2: Comparison of Baseline Characteristics between the Groups

Characteristics		Group A (n=50)
Age in Years	35-70	53.10±10.07
	35-50 years	23 (46.0%)
	51-70 years	57 (57.0%)
Gender	Male	22 (44.0%)
	Female	28 (56.0%)
Weight (kg)		68.36 ± 4.56
HbA1c (%)		8.72 ± 0.19

**Independent sample t-test, ** Chi square test, taking p-value≤0.05 as significant.*

After three months mean HbA1c in group B was significantly less than group A (8.00±0.13 vs. 7.42±0.08%; p-value=0.000). Mean change in HbA1c at three months from the values at presentation was significantly high in group B than group A (-0.70±0.25 vs. -1.33±0.17%; p-value=0.000). Data is given in Table 3.

Table 3: Comparison of Mean HbA1c at Various Intervals

HbA1C	Study Groups	N	Mean	Std. Dev.	P-value
At Presentation	Group A	50	8.71	0.20	0.284
	Group B	50	8.75	0.15	
At 3 Months	Group A	50	8.00	0.13	0.000
	Group B	50	7.42	0.08	
Mean Change	Group A	50	-0.70	0.25	0.000
	Group B	50	-1.33	0.17	

Intendent sample t-test, taking p-value ≤0.05 as significant.

Comparison of mean weight between the groups shows significantly less mean weight in group B at three months than group A (64.14±4.25 vs. 61.84±4.89 kg; p-value=0.014). Mean change in weight at three months was significantly high in group B than group A. Data is given in Table 4.

Table 4: Comparison of Mean Weight at Various Intervals

Weight	Study Groups	N	Mean	Std. Dev.	P-value
At Presentation	Group A	50	68.24	4.32	0.794
	Group B	50	68.48	4.83	
At 3 Months	Group A	50	64.12	4.25	0.014
	Group B	50	61.84	4.89	
Mean Change	Group A	50	-4.12	0.83	0.000
	Group B	50	-6.64	1.08	

Intendent sample t-test, taking p-value ≤0.05 as significant

When mean change in HbA1c and mean reduction in weight in both the groups was stratified for age and gender, it produced same significance for all the stratifications (p-value=0.000). Data is given in Table 5 and 6, respectively.

Table 5: Stratification of Mean Change in HbA1c for Age and Gender

Sub Group (Age/Gender)	Study Groups	N	Mean	Std. Deviation	p-value
35-50 Years	Group A	23	-.760	0.18	0.000
	Group B	21	-1.33	0.16	
51-70 Years	Group A	27	-.65	0.29	0.000
	Group B	29	-1.33	0.17	
Male	Group A	22	-0.68	0.29	0.000
	Group B	21	-1.29	0.18	
Female	Group A	28	-0.71	0.22	0.000
	Group B	29	-1.36	0.16	

Intendent sample t-test, taking p-value ≤0.05 as significant

Table 6: Stratification of Mean Change in Weight for Age and Gender

Sub Group (Age/Gender)	Study Groups	N	Mean	Std. Deviation	p-value
35-50 Years	Group A	23	-4.22	0.80	0.000
	Group B	21	-6.33	1.16	
51-70 Years	Group A	27	-4.04	0.85	0.000
	Group B	29	-6.86	0.99	
Male	Group A	22	-4.14	0.89	0.000
	Group B	21	-6.76	0.94	
Female	Group A	28	-4.11	0.79	0.000
	Group B	29	-6.55	1.18	

Intendent sample t-test, taking p-value ≤0.05 as significant

DISCUSSION

T2DM represents a complex metabolic disorder characterized by insulin resistance and impaired insulin secretion, resulting in elevated blood glucose levels. Managing this chronic condition necessitates a careful selection of treatment options to achieve optimal glycemic control. Among the arsenal of therapeutic interventions, metformin has long been established as a foundational therapy in T2DM management. However, the evolving landscape prompts a nuanced exploration of adjunctive therapies. This study endeavors to scrutinize and compare the effects of two such options, sitagliptin and empagliflozin, as add-on therapies to metformin in patients with T2DM. Given the existing controversies within the literature, this research is strategically designed to shed light on the comparative efficacy of these pharmacological interventions.

The mean age of participants in this study was recorded at 52.58±10.0 years, aligning closely with findings reported by Khan *et al*. (2022) in Pakistan, who observed a comparable mean age. However, contrasting data emerged from the study conducted by Mubashir *et al*. (2022)[9] in Pakistan, revealing a lower mean age of 51.83±6.30 years among their cohort. Notably, investigations conducted in Egypt by Zakaryia *et al*. (2023)[13] and in Sweden by Sabapathy *et al*. (2016)[14] reported slightly higher mean ages of 53.52±8.66 years (range 30-67 years) and 53.50±9.57 years (range 35-70 years), respectively. These variations in mean age across diverse populations carry implications for the understanding and management of T2DM. Age is a pivotal factor influencing the pathophysiology of T2DM, with potential implications for disease progression, treatment response, and associated comorbidities. The observed discrepancies underscore the need for tailored approaches in T2DM management, considering the demographic nuances that influence the disease's dynamics. As we navigate the intricacies of age-related

factors, these findings contribute to the evolving dialogue on personalized care strategies for individuals with T2DM across diverse geographic and ethnic landscapes.

In this study, the distribution of gender among participants revealed a notable female predominance, with males comprising only 43.0% (n=43), while females constituted the majority at 57% (n=57). This gender distribution aligns with similar trends observed in other studies, where Khan *et al*. (2022)[10] reported a female prevalence of 58.5%, Ferrani *et al*. (2013)[15] observed 61%, and Zakaryia *et al*. (59.8%).[13] Interestingly, Mubashir *et al*. (2022)[9] reported an inverse proportion, with males constituting 81.7% of their study sample. The gender composition in diabetes studies holds significance due to potential variations in disease presentation, progression, and response to therapeutic interventions.

The mean weight of patients at presentation in this study was documented as 68.36±4.56 kg, concomitant with a mean HbA1C (%) of 8.72±0.19. Notably, Mubashir *et al*. (2022)[9] had previously reported slightly lower mean values for both weight and HbA1C among their study sample at presentation, with values of 67.41±6.79 kg and 8.87±0.40%, respectively. These metrics of weight and HbA1C serve as critical indicators in the clinical landscape of T2DM. Weight, as a modifiable risk factor, is intricately linked to the management and progression of T2DM. The observed variations in mean weight between studies may reflect demographic, lifestyle, or regional differences that warrant further exploration.

Both study groups demonstrated comparability, lacking inherent differences in all baseline characteristics (p-value>0.05). This statistical insignificance suggests that, at the study's commencement, participants in both groups were well-matched in terms of key factors, ensuring a balanced distribution of baseline characteristics. Such equipoise is pivotal in clinical research, minimizing confounding variables and facilitating a more accurate assessment of the interventions' effects. The absence of significant differences at baseline enhances the internal validity of the study, bolstering the reliability of subsequent findings and conclusions drawn from the comparative analysis of the treatment groups.

At the three-month mark, Group B exhibited a significantly lower mean HbA1c compared to Group A (8.00±0.13 vs. 7.42±0.08%; p-value=0.000). Furthermore, the mean change in HbA1C from baseline was notably higher in Group B than in Group A (-0.70±0.25 vs. -1.33±0.17%; p-value=0.000). These findings align with results from Mubashir *et al*. (2022)[9], where the mean HbA1c after three months was 8.05±0.45 vs. 7.52±0.47% (p-value=0.000), and the mean change in HbA1c was -0.81 vs. -1.13% (p-value=0.000). Similarly, Zakaryia *et al*. (2022)[13] reported a significantly lower HbA1C at three months in Group B compared to Group A (8.27±1.91 vs. 7.18±1.31; p-value<0.001). However, in contrast, Khan *et al*. reported an insignificant difference in mean change in HbA1c between the groups as -0.82±1.57 vs. -0.97±0.68% (p-value=0.980). These findings collectively emphasize the consistency of improved glycemic control in Group B across multiple studies, underscoring the potential efficacy of the intervention in comparison to Group A.

The comparison of mean weight between the groups yielded significant differences at three months, with Group B demonstrating a notably lower mean weight compared to Group A (64.14±4.25 vs. 61.84±4.89 kg; p-value=0.014). Moreover, the mean change in weight at three months was significantly higher in Group B than in Group A. This observed trend persisted even when stratifying for age and gender, with consistent significance across all stratifications (p-value=0.000). These findings align closely with the results reported by Mubashir *et al*. (2022)[9], where the mean change in weight after three months was significantly higher in Group B than in Group A (-3.30 vs. -6.73; p-value=0.000). The convergence of results across studies reinforces the robustness of the observed weight-related outcomes associated with the respective treatment modalities (Sitagliptin + metformin in Group A and Empagliflozin + metformin in Group B). These insights contribute to the broader understanding of the interplay between medication regimens and weight dynamics in the context of Type 2 Diabetes Mellitus management.

CONCLUSION

In conclusion, our study reveals that empagliflozin leads to superior glycemic control and greater weight reduction compared to sitagliptin as add on therapy to metformin in patients T2DM. These findings emphasize the potential benefits of individualized treatment strategies for optimized outcomes in T2DM management.

LIMITATIONS

Limitations include limited follow-up duration may not capture long-term effects. Single-center design may limit generalizability.

SUGGESTIONS / RECOMMENDATIONS

Future research should address these limitations for a comprehensive understanding of treatment outcomes in Type 2 Diabetes Mellitus.

CONFLICT OF INTEREST / DISCLOSURE

Respondents are well-informed, with assured confidentiality. No conflicts of interest exist among the authors conducting the study.

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