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Comparative Assessment of Metformin vs GLP-1 RAs on Triad of Metabolic Syndrome Among Diabetics: An Observational Study

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Abstract

Background: Diabetes mellitus is a chronic metabolic syndrome (MetS) poses a significant global health challenge, necessitating effective management strategies. Among these, MetS plays a pivotal role, not only in glycemic control but also in improving overall patient quality of life. In the two cardinal anti-diabetic modalities entails Metformin and GLP-1 RAs. The impact of such drugs were assessed and compared alone and in combination for cardinal triad of metabolic syndrome among diabetics. **Methodology:** A total of 30-days observational cross-sectional study was conducted in the Endocrinology Unit of the Tertiary Care Hospital Peshawar. A total of 43 case histories were meticulously collected and analyzed out of total 20 were male and 23 were female. The data of day 1st and 30th were compared for three cardinal parameters of MetS like obesity in term of weight in kg, BMI, cholesterol; LDL, and blood glucose in term of HbA1c. A Brown-Forsythe test and One-way ANOVA by using Graph Pad Prism 8.0.2 and Microsoft Excel (Professional Plus 2016) was applied and the p-value < 0.05 was kept standard. **Results:** Findings of this study indicates that combination therapy involving Metformin and GLP-1 RA drugs yielded a substantial impact on MetS and the *p*-value based on Brown-Forsythe test was < 0.05. Besides, the impact of alone drugs like Metformin, liraglutide and semaglutide were statistically in-significant (p-value > 0.05) based on One-way ANOVA while significant based on Brown-Forsythe test. These results highlight the potential synergy of combination therapy in achieving remarkable MetS management outcomes for diabetics. **Conclusion:** In summary, this research contributes valuable gaining a deeper understanding of the multifacetedlandscape of MetS in diabetes treatment, emphasizing the potential advantages of personalized treatment strategies and combination therapy.

1. Introduction

Diabetes mellitus (DM) stands as a formidable global health challenge, characterized by its chronic nature and intricate interplay of metabolic dysregulation. According to the International Diabetes Federation, an estimated 463 million people were living with diabetes worldwide in 2019, and this number is projected to rise to 700 million by 2045. The chronicity of DM and its potential complications necessitate an ongoing exploration of effective therapeutic approaches to manage the condition and its associated co-morbidities. Diabetes mellitus is a metabolic disorder marked by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1-2].

Overall 8.3% populations worldwide are suffering from diabetes with equal rates in males and females and is 7th leading cause of death all over the world [3].Metabolic syndrome (MetS) is substantially involved in the DM which is characterized by five major contributing factors entail; obesity, hypertension, raised triglycerides, reduced HDL, and raised fasting blood glucose [3]. Interestingly, the IDF declared that three out of five can also be considered as MetS. The triad of MetS enfolds obesity in term of BMI and weight in kg, LDL under the heading of cholesterol and blood glucose level in term of HbA1c was targeted in this study [4-5].

The pharmacological management of diabetes primarily involves two broad categories of drugs: oral antidiabetic agents and insulin. Among the oral antidiabetic agents, metformin has emerged as a gold-standard cornerstone in the treatment of type 2 diabetes (T2D). Its efficacy, safety profile, and ability to address both insulin resistance and hyperglycemia make it a first-line therapy for many patients [6-7].

Notably, beyond its glucose-lowering effects, metformin has garnered attention for its potential role in weight reduction, a crucial aspect of managing diabetes and its associated cardiovascular risk factors

Metformin, a biguanide, has been a stalwart in diabetes management for decades. Its mechanisms of action include suppression of hepatic glucose production, improvement of insulin sensitivity, and reduction of intestinal glucose absorption [8]. While its primary indication is glucose control, emerging evidence suggests that metformin may exert favorable effects on body weight, making it a promising therapeutic option for individuals with diabetes who struggle with overweight or obesity [9-10].

In recent years, a new class of drugs, namely GLP-1 receptor agonists (GLP-1 RAs), has garnered attention for its multifaceted benefits in diabetes management. GLP-1 is an incretin hormone that stimulates insulin secretion and inhibits glucagon release, contributing to glucose homeostasis. GLP-1 RAs, as synthetic analogs of GLP-1, offer a novel approach to diabetes treatment [7]. GLP-1 RAs function by mimicking the physiological actions of GLP-1. They enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and promote satiety [11]. Beyond glycemic control, GLP-1 RAs exhibit additional benefits such as cardiovascular risk reduction and weight loss. Understanding the mechanisms underlying their effects, their convenient modes of administration, and their impact on MetS provides valuable insights into their potential as pivotal components in the armamentarium against diabetes. It is imperative to note that such a study, exploring the specific impact of metformin and GLP-1 receptor agonists on MetS among individuals with diabetes, has not been conducted in Pakistan to date. By undertaking this research in the context of the unique demographic and healthcare landscape of Pakistan, we aim to contribute valuable insights that may inform more tailored and effective diabetes management strategies for the diverse population in this region [12].

2. Methodology

2.1. Study Design and Duration

A month (July-August 2023) cross-sectional study conducted in the OPD ward under Consultant level Endocrinologist and diabetologist in one of the Tertiary Care Hospital, Peshawar.

2.2. Inclusion and Exclusion Criteria

The obese diabetics included in the study of both gender of age > 18 years. Patients who doesn't have a follow up record during the period of their treatment. Besides, other endocrine disorders such as acromegaly and cushsing syndrome cases were excluded from the study [13].

2.3. Study Variables

The age, gender, date of admission, address, present history of illness and physical assessment were noted. Likewise, the triad of MetS; obesity in term of body mass index (BMI) and weight in kg, low density lipoprotein (LDL), and blood glucose level in term of HbA1c was evaluated in this study.

2.4. Instruments for Data Collection

The data of the patients was collected by using the proforma recommended by the Department of Pharmacy Abasyn University Peshawar from the book "Essence of Clinical Pharmacy" [14].

2.5. Ethical Approval and Data Analysis

This study was conducted in the PharmD Clinical Clerkship of the first author. After receiving a proper permission from the hospital. Besides, the patient informed consents were signed. The data was mostly collected by asking questions from the patients, patient attendants, nurses, and also collected from the files of the patients. After collection, the data was arranged carefully and analyzed through Microsoft Excel (Professional Plus 2016). The Brown-Forsythe test and One-way ANOVA by using GraphPad Prism 8.0.2 was applied and the p-value < 0.05 was kept standard. The

scheme of this study is depicted in the (Figure 1.1).

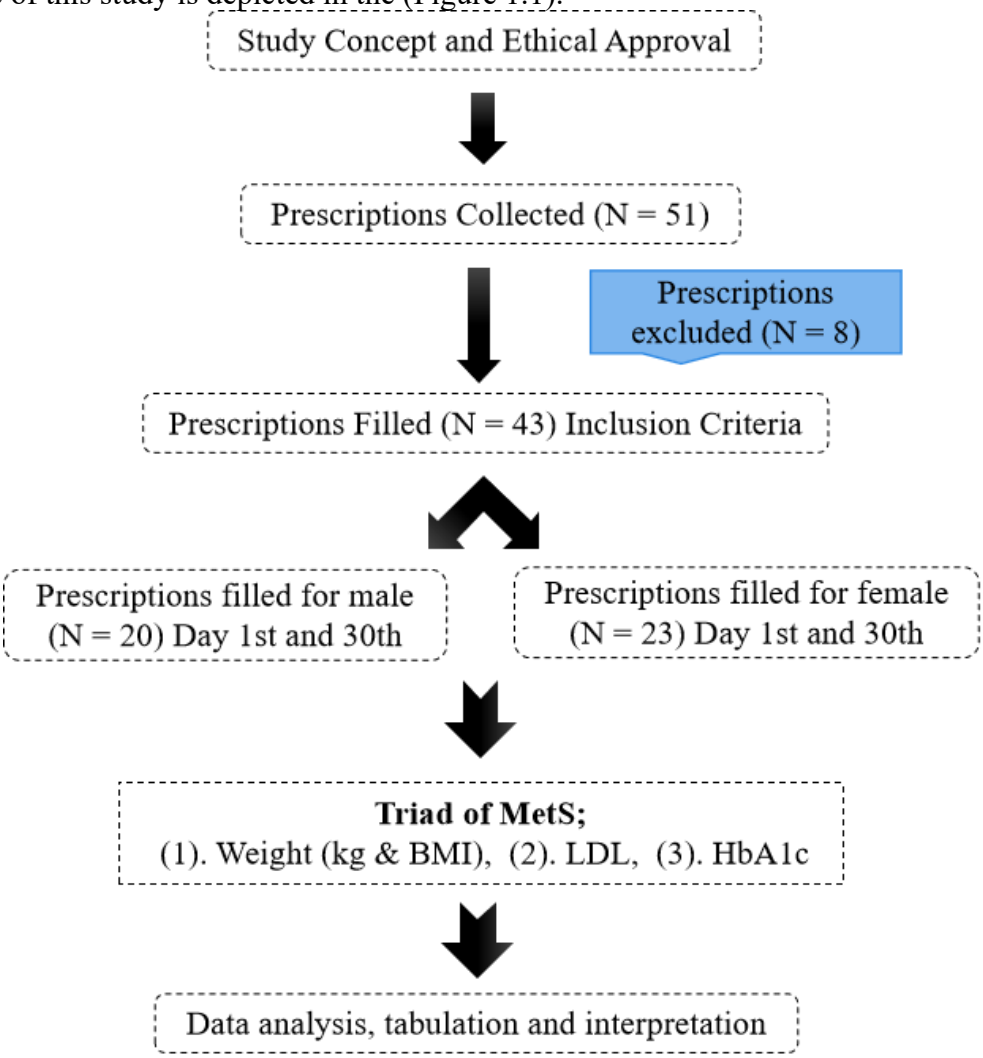
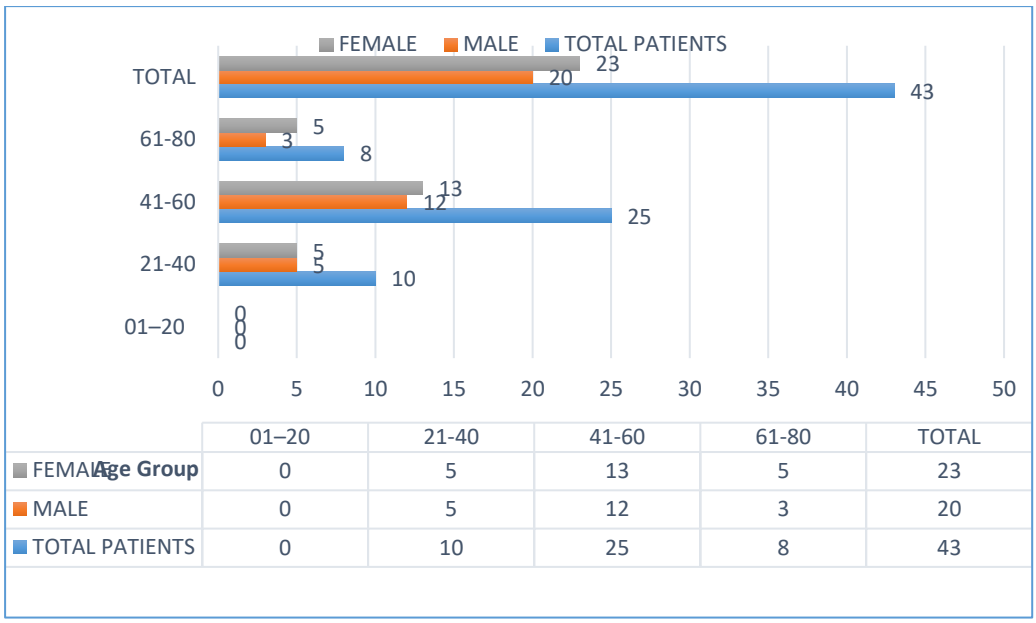


Figure 1.1: Flow chart of the study

3. Results

Based on methodology this chapter comprehensively summarizes the results of the study in which Figure 1.2, depicts a comprehensive comparison between male and female patients involved in the study. The research encompassed a total of 43 patients, with 20 identified as male and 23 as female participants.



Age Group	01–20	21-40	41-60	61-80	TOTAL
FEMALE	0	5	13	5	23
MALE	0	5	12	3	20
TOTAL PATIENTS	0	10	25	8	43

Figure 1.2: Gender and age-wise classification of the patients in the study (N = 43)

3.1. Metformin Impact on Diabetics

Table 1.1 summarizes the effects of Metformin on patients over a 30th day, assessing various parameters, including weight in kg, BMI, LDL, and HbA1c. This table provides a comprehensive view of the treatment's impact on these key metrics. Further comparative assessment is also displayed in the Figures 1.3-1.6.

Table 1.1: Metformin impact on diabetes different laboratory parameters on day 1st and 30th

Day 1 weight (kg)	**Day 30 weight (kg)**	**Day 1 BMI**	**Day 30 BMI**	**Day 1 LDL**	**Day 30 LDL**	**Day 1 HbA1c**	**Day 30 HbA1c**
118	114	33	31	106	132	6.2	5.7
78	76	30	29	62	133	6.7	6.3
86	84	36	35	128	133	7.2	7
70	68	36	34	115	76	8.2	7.5
67	64	27	25	71	105	10.5	9.4
78	76	35	33	80	80	12.5	10.2
80	79	30	30	172	169	7.1	6.8
85	83	29	28	148	120	5.6	5.2
Mean							
82.9	80.3	31.9	30.6	110.7	113.3	8.48	7.49

3.2. Liraglutide Impact on Diabetics

Table 1.2 delves into the influence of Liraglutide on patients throughout 30 days duration, evaluating a range of factors, such as weight, BMI, LDL, and HbA1c. Besides, Figures 1.3-1.6 offers a comprehensive perspective on how the treatment affects these critical measurements.

Table 1.2: Liraglutide impact on diabetes various biomarkers on day 1st and 30th

Day 1 weight (kg)	**Day 30 weight (kg)**	**Day 1 BMI**	**Day 30 BMI**	**Day 1 LDL**	**Day 30 LDL**	**Day 1 HbA1c**	**Day 30 HbA1c**
79	73	37	33	214	170	9.1	8.4
93	86	43	40	119	187	7.3	6.2
112	109	43	41	134	120	12.1	8.7
77	74	33	31	89	76	9.6	8.4
72	70	32	31	200	180	11.8	9
81	79	30	29	130	146	11.2	10.3
85	83	27	26	89	46	9	8.1
Mean							
92.1	88.3	36.4	34.3	129.1	109.2	9.79	8.25

3.3. Semaglutide Impact on Diabetics

Table 1.3 entails the impact of Semaglutide on patients over a 30-day period, assessing a variety of factors, including weight, BMI, LDL, and HbA1c. Figures 1.3-1.6 depicts an extensive insight into how the treatment influences these important measurements.

Table 1.3: Semaglutide impact on diabetes different Biomarkers on day 1st and 30th

Day 1 weight (kg)	**Day 30 weight (kg)**	**Day 1 BMI**	**Day 30 BMI**	**Day 1 LDL**	**Day 30 LDL**	**Day 1 HbA1c**	**Day 30 HbA1c**
80	76	33	31	114	109	10.2	8.5
90	89	27	27	75	83	7.9	7
78	76	30	29	123	130	6.2	5.9
94	88	39	37	111	105	5.9	6
78	76	30	29	123	120	6.2	5.9
107	103	37	35	152	118	5.9	5.4

132	120	40	36	257	140	6.5	5.8
Mean							
100.13	95.80	36.87	34.60	128.47	110.13	7.53	6.62

3.4. GLP-1 RAs + Metformin impact on diabetics

Table 1.4 investigates the effects of GLP-1 RAs + Metformin on patients over a 30-day timeframe, evaluating a range of factors, including weight, BMI, LDL, and HbA1c. Figures 1.3-1.6 reflects a comprehensive perspective on how the treatment affects these crucial measurements**.**

Table 1.4: Metformin + GLP-1 RAs effect on diabetes different Biomarkers on day 1st and 30th

Day 1 weight (kg)	**Day 30 weight (kg)**	**Day 1 BMI**	**Day 30 BMI**	**Day 1 LDL**	**Day 30 LDL**	**Day 1 HbA1c**	**Day 30 HbA1c**
79	73	37	33	214	70	9.1	8.4
84	80	31	28	98	101	9.2	8.1
81	75	32	29	55	57	8.4	6.8
113	109	38	36	92	85	9.6	7.4
80	85	33	31	114	109	10.2	8.5
197	132	45	43	102	120	8.5	8.2
Mean							
103.86	91.29	35.86	33.14	116.00	87.86	9.03	7.76

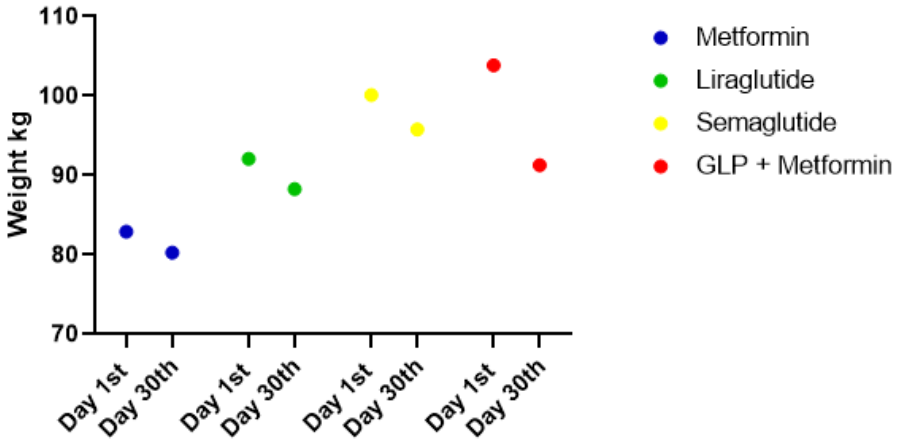


Figure 1.3: Comparative impact of Metformin, GLP-1 RAs individually and Combo on weight (kg)

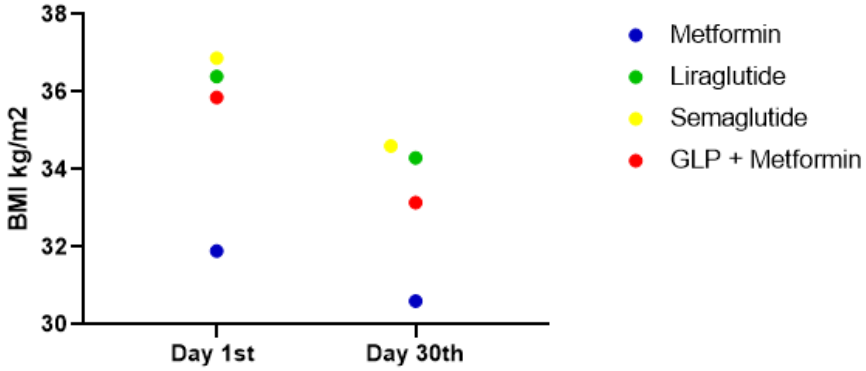


Figure 1.4: Relative effect of Metformin, GLP-1 RAs individualy and Concomitant on BMI (kg/m^2)

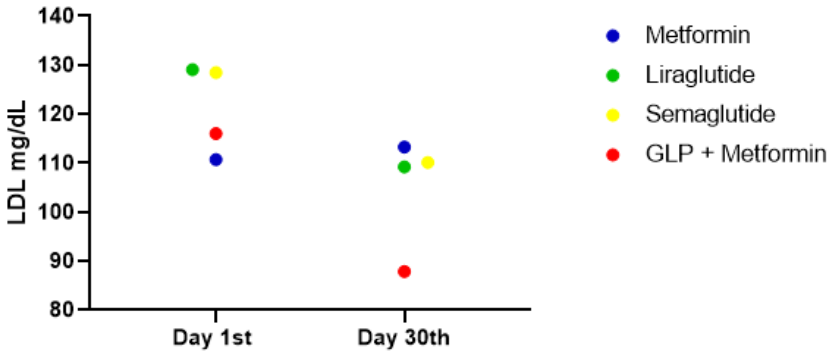


Figure 1.5: Comparative impact of Metformin, GLP-1 RAs individualy and Coexist on LDL level (mg/dL)

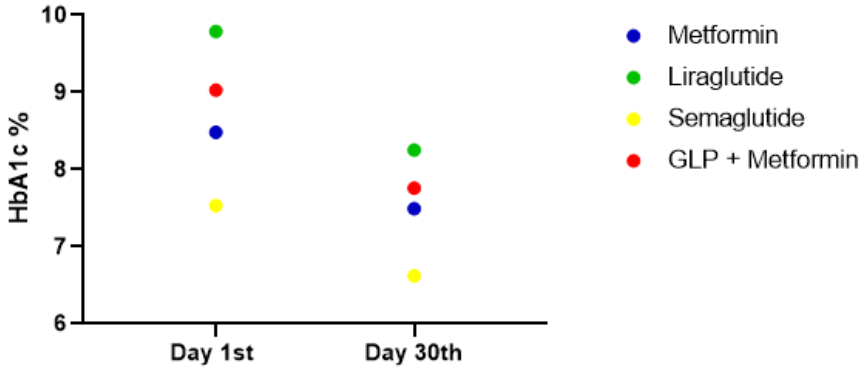


Figure 1.6: Comparative impact of Metformin, GLP-1 RAs individualy and Combo on HbA1c (%)

The overall impact of Metformin with GLP-1 RAs is very significant comparatively. Figure 1.7 summarizes the synergy of combo on triad of MetS.

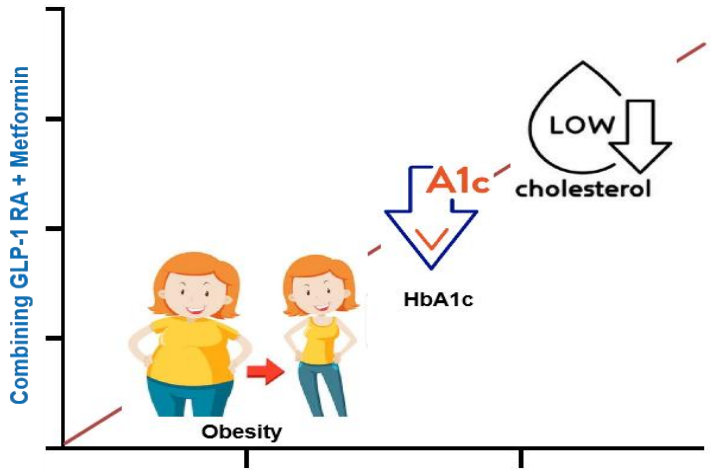


Figure 1.7: A substantial impact of GLP-1 RAs + Metformin on alleviation of MetS triad

Discussion

The studies conducted by Nauck *et al*. (2013) [15] and Jensterle Sever *et al*. (2014) [16] both examined the effects of GLP-1 receptor agonist drugs, specifically liraglutide, and Metformin on weight loss and blood glucose in diabetics. Nauck *et al*. (2013) found that liraglutide led to significant weight loss compared to Metformin monotherapy, with liraglutide 1.2 mg and 1.8 mg demonstrating superior outcomes. In this study it has been observed similar weight loss results for Metformin and liraglutide obtained, although the effect on BMI was not as pronounced as in Nauck *et al*.'s study. This suggests that while both drugs may lead to weight loss, the impact on BMI may vary.

Jensterle Sever *et al*. (2014) further investigated the effects of Metformin and liraglutide, both individually and in combination, on weight loss. Their study showed that the combination therapy (COMBO) of Metformin and liraglutide was significantly more effective in reducing weight, and BMI, compared to the individual therapies [17]. Our findings supports this, because we observed a substantial weight loss with COMBO therapy compared to the individual therapies. This emphasizes the potential synergistic effects of combining these two treatments for better weight management [18].

The study conducted by Jensterle, Salamun, *et al*. (2015), liraglutide was found to be superior to Metformin in reducing weight and BMI. The results our current study align with their findings regarding weight loss, but again there is a discrepancy in the impact on BMI reduction. This indicates that while liraglutide may lead to weight loss, its effect on BMI might vary among different patient populations [19].

Jensterle *et al*. (2016) explored the combination therapy of Metformin and liraglutide in comparison to liraglutide alone. Their study showed that COMBO therapy resulted in greater weight loss and BMI reduction. Our result supports this trend, with COMBO therapy showing the most significant weight loss and BMI reduction.

Keskin & Yaprak's study (2022) highlighted the substantial weight loss and BMI reduction associated with liraglutide compared to Metformin [20]. Our current study results are consistent with their findings regarding weight loss but do not show the same level of efficacy in reducing BMI. This suggests that while liraglutide may be more effective in promoting weight loss, its impact on BMI may be influenced by various factors [21].

Additionally, the results compared with Lin *et al*. (2023) for GLP-1 RAs on weight loss. Their meta-analysis demonstrated a significant decrease in body weight in patients receiving GLP-1 receptor agonists compared to Metformin [22]. In the current study, we observed weight loss in the Semaglutide group, which aligns with Lin *et al*.'s findings.

In the study conducted by Khunti *et al*. (2021), a significant decrease in HbA1c

levels was observed among the patients, ranging from 0.8% to 1%. Similarly, Tofé *et al*. (2019) reported a baseline HbA1c of 8.18% in 735 diabetic patients, with an average follow-up period resulting in a reduction of approximately 0.93% [23]. In our study, comprising 43 diabetic patients and employing a therapy regimen involving metformin and GLP-1 receptor agonists, we observed a more pronounced decrease in HbA1c levels, amounting to 1.2%. These findings highlight the effectiveness of the treatment approach in achieving substantial reductions in HbA1c, underscoring the potential impact of metformin and GLP RA drugs in managing diabetes.

The study conducted by Wulffele et al. (2004) involving 3074 diabetic patients demonstrated noteworthy findings on lipid profiles. After receiving metformin for 4 to 6 weeks, there was a substantial decrease in both cholesterol (-0.26 mmol) and LDL cholesterol (-0.22 mmol) (1). Similarly, Solymár *et al*. (2018) conducted a study with 1541 diabetic patients receiving metformin, revealing consistent outcomes [24-26]. Following the therapy, a significant reduction was observed in both cholesterol (-0.184 mmol/L) and LDL cholesterol (-0.182 mmol/L).

In alignment with these studies, our investigation, focusing on patients treated solely with metformin, mirrored the observed trends. We found a significant decrease in cholesterol levels, akin to Wulffele *et al*. (2004) and Solymár *et al.* (2018), emphasizing the consistent lipid-lowering effects of metformin in diabetic patients [27].Similar study was also performed by Pirzada et al (2025) showing promising decrease in HbA1c levels was observed among the patients, ranging from 0.5% to 1% [28-29].

These findings underscore the distinct weight loss profiles associated with these treatments. Combination therapy, which involves both Metformin and GLP-1 RA drugs, emerged as a potent approach for achieving substantial weight loss in diabetic patients, with the observed weight reduction far surpassing that of individual therapies [30]. This underscores the potential advantages of personalized treatment strategies to optimize weight management in diabetic patients, taking into account factors such as medication type and patient response.

Conclusion

In summation, the investigation into the MetS of GLP-1 RAs drugs versus Metformin in diabetic patients has yielded valuable insights into the realm of diabetes management. This study, conducted with careful consideration of relevant literature and the collection of real-world patient data, offers significant contributions to our understanding of the efficacy of these treatments. The findings presented in this study underscore the complexity of MetS management in diabetic patients. The research demonstrates that both GLP-1 RA drugs, such as liraglutide and semaglutide, and Metformin alone can contribute to MetS in diabetic individuals. However, the extent and significance of the MetS vary among different treatment regimens. Combination therapy, which involves the simultaneous administration of Metformin and GLP-1 RA drugs, emerged as a particularly promising approach in achieving substantial MetS alleviation. The observed traid of MetS reduction in this group far exceeded that of individual therapies, underscoring the potential benefits of tailored treatment strategies that consider both medication type and patient response. While the efficacy of GLP-1 RA drugs in MetS alleviation has been established in this study, it is important to note that the impact on BMI reduction may differ among patient populations and treatment modalities. This highlights the need for a personalized approach to diabetes management, considering individual patient characteristics and preferences. Moreover, this study highlights the importance of further research in this field to elucidate the mechanisms underlying the variations in treatment outcomes. Future studies may delve into the interplay between genetics, lifestyle factors, other domains of MetS and the choice of medication to optimize MetS management for diabetic patients. In the context of healthcare delivery, the insights gained from this study provide healthcare professionals with valuable information to make informed decisions when tailoring

treatment plans for diabetic patients. This, in turn, may lead to more effective and patient-centered strategies for achieving optimal glycemic control and MetS management in diabetic individuals.

Study Limitations and Recommendations

However, this research acknowledges its limitations, including the short one-month study duration and the omission of other classes of oral antidiabetic drugs. Future research endeavors are recommended to expand data collection, incorporate longer-term follow-ups, and encompass a wider range of antidiabetic medications. Furthermore, investigating additional clinical parameters other domains of MetS and adopting a patient-centered approach can provide a more holistic understanding of diabetes management.

Conflict of Interest

Nil

Acknowledgment

We are acknowledged to well-wishers globally.

Data availability

The raw data can be available from first author upon request.

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