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PHARMACOLOGICAL APPROACHES TARGETING INCRETIN HORMONES IN DIABETES MANAGEMENT

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ABSTRACT

OBJECTIVE: Changes in glycemic control, as measured by HbA1c levels, was the main end measures. Changes in body weight was secondary end measures. **METHODOLOGY:** Baseline evaluations were performed, which included demographic data, glycated hemoglobin levels (HbA1c) and body weight were measured. Comparisons were made with the values obtained after 12 weeks of intervention **RESULTS:** The value of HbA1C and body weight was determined at baseline and after 12 weeks of intervention and the findings had revealed that at baseline the value of HbA1C of group A was 7.8%±2.2 and body weight was 80.2kg±2.5 that had significantly p<0.001 reduced to 5.2%±2.5 and 74.3kg ± 2.9. The values of HbA1C in group B at baseline was 7.5%±3.2 that had significant p<0.001 reduced to 5.7%±2.4 and average weight that was 79.09kg±3.2 was reduced to 75.4kg±1.85 (p<0.001). In group C also the effects of standardized treatment had provided significant findings and the differences in the mean glycated hemoglobin levels and body weight was found to be significant p<0.001 **CONCLUSION :** Overall, incretin-based therapeutics provide patients with type 2 diabetes creative and efficient treatment choices, offering promise for improved disease control and quality of life. The advantages and safety profiles of these medicines in a larger patient population will be completely clarified by more study and long-term investigations.

KEYWORDS: Diabetes Mellitus, Incretins, Glycated Hemoglobin

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INTRODUCTION

Type 2 diabetes (T2D) is a severe global health concern, impacting about one in every eleven persons globally and putting a significant strain on healthcare systems. Its link to heart disease and stroke, two of the main causes of death, magnifies its influence on mortality rates[1]. T2D is complicated by insulin resistance, inefficient pancreatic islet activity, and disturbances in hormonal signaling to the brain, all of which lead to obesity and metabolic dysfunction. Current therapies focus on specific components of the condition, such as increasing insulin levels or sensitivity[2-3]. However, the complex interaction of numerous elements necessitates a more sophisticated and comprehensive strategy to combating T2D[4]. Although bariatric surgery has shown potential in treating T2D, its invasiveness and financial constraints limit its broad use. As a result, there is an urgent need to discover noninvasive pharmacological medicines that can mimic the benefits of surgery by targeting several tissues simultaneously. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic peptide (GIP), have lately received attention due to their extensive effects on diabetes-related tissues[5-6]. The

weakening of the incretin effect in T2D, which is responsible for a major amount of postprandial insulin production, shows that it plays a role in disease progression[7]. Furthermore, glucagon, which was previously known for its glycemic regulation, is now known for its role on energy metabolism, encouraging study into targeting the glucagon receptor to treat metabolic disorders. Incretin hormones, particularly GLP-1 and GIP, have emerged as attractive targets for diabetes management in recent years. These hormones not only govern insulin secretion and glucose levels, but they also control appetite, satiety, and total energy balance[8]. Addressing the reduced incretin impact in T2D may hold the key to understanding the disease's underlying causes and providing a more comprehensive strategy to treatment[9]. Furthermore, research has discovered that glucagon, previously thought to be only an insulin antagonist, plays an essential function in metabolic control. Efforts to modify glucagon receptor activation have opened up new avenues for therapeutic approaches that enhance glucose control and have implications for weight management and general metabolic health[10]. The importance of incretin hormones and their possible role in T2D management has sparked the interest of both the scientific and pharmacological realms[11]. To completely understand the therapeutic potential of GLP-1 receptor agonists and DPP-4 inhibitors, it is critical to investigate their action, effectiveness, and safety mechanisms. These findings will open the path for developing novel pharmacological medicines that can thoroughly address the difficulties of T2D, perhaps duplicating the favorable outcomes seen with bariatric surgery but without the invasiveness and financial restraints. With the increasing global incidence of T2D and its related health and economic consequences, there is an urgent need for innovative and effective treatment options. Investigating incretin-based therapeutics provides a viable path forward in diabetes care. This work intends to give the scientific community with critical insights to promote the development of safer, more efficient, and patient-friendly therapy alternatives for people living with T2D by shining light on the debates surrounding these gut-derived peptides. Finally, the findings of this study have the potential to dramatically improve the quality of life for diabetics while also reducing the global effect of this common metabolic condition.

METHODOLOGY

Study Design A randomized controlled trial was performed and participants were divided into three groups. **Study Setting:** Suleman Roshan Medical College Hospital **Target Population** Adult patients diagnosed with type 2 diabetes and seeking treatment at Suleman Roshan Medical College Hospital were the study's target group. Individuals having a history of severe cardiovascular illness, chronic renal disease, liver failure, or any other serious comorbidity were not allowed to participate in the trial. **Sample Size:** A sample size of n=150 T2DM patients divided into three group n=50 patient in each group were recruited for the purpose of the study. **Grouping of Patients Group A:** GLP-1 receptor agonists, namely Exenatide, were delivered subcutaneously to patients in Group A. The starting dose was 5 micrograms twice day, which was gradually increased to 10 micrograms twice daily as tolerated and necessary for good glycemic control. **Group B:** DPP-4 inhibitors, especially Sitagliptin, were given to subjects. The starting dose was 100 mg once day, which was increased to a maximum dose of 100 mg twice daily based on individual response and tolerability. **Group C:** The control group, Group C, received normal diabetes treatment. This includes lifestyle changes, dietary counselling, and diabetes self-management instruction. The standard of therapy also included the use of typical oral hypoglycemic medications, such as metformin and sulfonylureas, as determined by the treating physicians. If glycemic objectives were not met with oral medicines alone, insulin treatment may have been commenced. **Inclusion and Exclusion Criteria** Participants were eligible for this randomized controlled trial if they had a confirmed diagnosis of type 2 diabetes, were between the ages of 18 and 65, and were prepared to provide informed permission and fulfil the research conditions. Individuals with a history of severe cardiovascular disease, chronic kidney disease at Stage 4 or higher, severe liver dysfunction, uncontrolled hypertension, a history of pancreatitis, pregnancy or breastfeeding, and those using other investigational drugs or participating in

another clinical trial within the previous three months, on the other hand, were excluded from the study. **Data Collection Procedure** Data collection began once all research participants provided informed consent. Baseline evaluations were performed, which included demographic data, glycated hemoglobin levels (HbA1c) and body weight were measured. Comparisons were made with the values obtained after 12 weeks of intervention **Outcome Measures** Changes in glycemic control, as measured by HbA1c levels, was the main end measures. Changes in body weight was secondary end measures. **Ethical Consideration** Suleman Roshan Medical College examined and approved the research protocol. Before being included in the experiment, all study participants provided informed permission. Throughout the study, participants' anonymity and privacy were scrupulously observed. The trial was carried out in conformity with the principles of the Helsinki Declaration and Good Clinical Practice standards. Any adverse events that occurred during the study were immediately reported to the IRB and the applicable regulatory authorities.

RESULTS

The demographic description of the participants had revealed that the average age of all the participant's included in the study was 53.54±2.14 years and the mean weight was 79.2±4.2years. The detailed illustration regarding the baseline characteristics of the participants group wise were provided in table 1 as under:

Table 1 Demographic Characteristics of Participants included in the study

Variables	Mean age in years ± SD	Level of significance p-value	Mean body Weight in kg ± SD	Level of significance p-value
Group A	52.63±1.58	>0.05	80.2±2.5	>0.05
Group B	54.87±2.3		79.09±3.2	
Group C	53.44±2.56		79.4±1.5	

Inferential statistics revealed that at baseline the characteristics of participants in all the three groups were no significantly different p>0.05, hence suggesting that baseline the division of the patients in all the three group was completely balanced. Further the value of HbA1C and body weight was determined at baseline and after 12 weeks of intervention and the findings had revealed that at baseline the value of HbA1C of group A was 7.8%±2.2 and body weight was 80.2kg±2.5 that had significantly p<0.001 reduced to 5.2%±2.5 and 74.3kg ± 2.9. The values of HbA1C in group B at baseline was 7.5%±3.2 that had significant p<0.001 reduced to 5.7%±2.4 and average weight that was 79.09kg±3.2 was reduced to 75.4kg±1.85 (p<0.001). In group C also the effects of standardized treatment had provided significant findings and the differences in the mean glycated hemoglobin levels and body weight was found to be significant p<0.001. (Table 2)

Table 2 Levels of glycated hemoglobin and weight at baseline and after 12 weeks of intervention

Variables	HbA1C±SD Baseline	HbA1C±SD Week 12	Level of Significance	Weight in Kg Baseline	Weight in Kg Week 12	Level of Significance
Group A	7.8%±2.2	5.2%±2.5	p<0.01	80.2kg±2.5	74.3kg ± 2.9	p<0.01
Group B	7.5%±3.2	5.7%±2.4		79.09kg±3.2	75.4kg±1.85	
Group C	7.64%±2.5	6.1%±2.3		79.4kg±1.5	75.7kg±2.1	

Further between the group comparison was performed that revealed that group A had shown greater improvement than group B and C with a significant reduction p<0.05 in the levels of glycated hemoglobin and weight followed by improvement in group B. The illustration of findings were provided in table 3 as under:

Table 3 Levels of glycated hemoglobin and weight between group comparison

Variables	HbA1C±SD Week 12	Level of Significance	Weight in Kg Week 12	Level of Significance
Group A	5.2%±2.5	p<0.01	74.3kg ± 2.9	p<0.01
Group B	5.7%±2.4		75.4kg±1.85	
Group C	6.1%±2.3		75.7kg±2.1	

DISCUSSION

The study's findings revealed that the characteristics of participants in all three groups (Group A: GLP-1 receptor agonists, Group B: DPP-4 inhibitors, and Group C: control group receiving standard diabetes care) were not significantly different at baseline (p<0.05), indicating a well-balanced distribution of patients among the groups. Further analyses were carried out to assess the impact of the various therapies on glycated hemoglobin (HbA1C) levels and body weight over the course of the 12-week intervention. Group A had a mean HbA1C of 7.8% (±2.2) and a mean body weight of 80.2 kg (±2.5) at the start. Following 12 weeks of GLP-1 receptor agonist therapy, HbA1C levels fell considerably to 5.2% (±2.5), and average body weight decreased to 74.3 kg (±2.9) (p>0.001). Similarly, in Group B, the baseline HbA1C was 7.5% (3.2), and the mean body weight was 79.09 kg (±3.2). After 12 weeks of DPP-4 inhibitor therapy, HbA1C was reduced to 5.7% (±2.4), and average body weight was reduced to 75.4 kg (±1.85) (p<0.001). Standard diabetes management resulted in a substantial decrease in HbA1C levels and body weight in Group C (control group) (p<0.001). Between-group comparisons revealed that Group A improved the greatest in both glycated hemoglobin levels and body weight, followed by Group B and lastly Group C (p<0.05). The findings show that GLP-1 receptor agonists (Group A) were more successful than DPP-4 inhibitors (Group B) and routine diabetic therapy (Group C) in improving glycemic control and weight loss. Overall, the outcomes of the trial confirm the higher efficacy of GLP-1 receptor agonists, especially Exenatide, in improving glycemic control and facilitating weight reduction when compared to DPP-4 inhibitors (Sitagliptin) and routine diabetes therapy alone. These findings have important implications for type 2 diabetes care, since GLP-1 receptor agonists may provide a more effective therapeutic alternative for individuals seeking better glucose control and weight management. Glucagon-like peptide-1 (GLP-1) receptor agonists provide considerable advantages in the treatment of type 2 diabetes[12]. GLP-1 receptor agonists provide a novel approach to diabetes therapy, with benefits that go beyond glucose control. These medicines, in addition to increasing insulin secretion and decreasing glucagon release, increase satiety and reduce stomach emptying, resulting in weight reduction and better metabolic parameters[13-14]. The beneficial effects on blood pressure and cholesterol levels underscore the potential of GLP-1 treatment in treating cardiovascular risk factors in type 2 diabetic patients[15]. Incretin hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, are important in post-meal glucose management[16-17]. Patients with type 2 diabetes, on the other hand, frequently have poor responses to GIP. Incretin-based medicines such as GLP-1 receptor agonists and DPP-4 inhibitors have emerged as promising treatment alternatives. GLP-1 receptor agonists act similarly to natural GLP-1, boosting insulin release in a glucose-dependent manner while inhibiting glucagon secretion without causing hypoglycemia[18-19]. These drugs, which are available as human counterparts (e.g., liraglutide) or synthetic exendin-based mimetics (e.g., exenatide), also delay stomach emptying, which may promote weight loss. DPP-4 inhibitors, such as sitagliptin and saxagliptin, on the other hand, impede the breakdown of endogenous incretin hormones, boosting their impact on glycemic control[20].

Overall, GLP-1 receptor agonists and DPP-4 inhibitors have the potential to improve postprandial and fasting glucose control while perhaps maintaining beta-cell function in individuals with type 2 diabetes[21]. Their usage as adjuncts to conventional medications may halt disease development and improve blood pressure, making them attractive complements to diabetes control program.

A randomized controlled trial strategy was used in this investigation, which allowed for a thorough assessment of the impact of incretin-based therapy on glycemic control, body weight, and other clinical outcomes in type 2 diabetes patients. Randomization enabled a well-balanced distribution of participants across the three research groups, which improved the findings' validity. The intervention was only in place for a brief period of time (12 weeks), which might have prevented the study from accurately capturing the long-term impacts of incretin-based treatments. Furthermore, the study sample could not accurately reflect the broad group of people with type 2 diabetes, which would limit the generalizability of the findings. Additionally, the study did not thoroughly evaluate any particular adverse effects, and further research into the long-term safety of incretin-based treatments might be beneficial.

CONCLUSION

In conclusion, this study emphasizes the therapeutic potential of incretin-based treatments, particularly GLP-1 receptor agonists and DPP-4 inhibitors, in the treatment of type 2 diabetes. The results show that these substances can successfully enhance glycemic management, encourage weight reduction, and perhaps maintain beta-cell activity. The study highlights the benefits of these treatments but also acknowledges their possible drawbacks, highlighting the necessity of thorough monitoring and taking into account specific patient variables. Overall, incretin-based therapeutics provide patients with type 2 diabetes creative and efficient treatment choices, offering promise for improved disease control and quality of life. The advantages and safety profiles of these medicines in a larger patient population will be completely clarified by more study and long-term investigations.

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