Comparison of Quintuple Oral Anti-Diabetes Regimen with Standard Triple Oral Regimen in Managing Uncontrolled Type 2-Diabetes Mellitus: A Retrospective Controlled Cohort Study

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ABSTRACT

Introduction: This study aimed to assess the efficacy of incorporating a combination of SGLT2 inhibitors (SGLT2i) and thiazolidinediones (TZD) into the current triple therapy regimen (metformin+sulphonylurea+DPP4 inhibitors) for individuals with diabetes. The primary objective was to compare the outcomes of the active group, which received the supplementary treatment, with the control group, which followed the standard triple regimen without additional medications.

Methods: Participants were allocated into two groups: the active group and the control group. The active group received SGLT2i and TZD in addition to their existing triple therapy, while the control group continued with the standard triple regimen. Various clinical parameters including blood pressure, glycemic control, and lipid profiles were assessed and compared between the two groups.

Results: The active group demonstrated significant improvements in multiple clinical parameters. Notably, there were reductions in systolic blood pressure, diastolic blood pressure, HbA1c levels, and total cholesterol levels. In contrast, the control group showed more modest improvements in HbA1c levels and total cholesterol levels, but not as significant as those observed in the active group. The active group exhibited superior outcomes in terms of glycemic control, blood pressure control, and lipid profiles compared to the control group.

Conclusion: The incorporation of SGLT2i and TZD into the preexisting triple therapy regimen resulted in notable enhancements in glycemic regulation, blood pressure, and lipid profiles in individuals with diabetes. These findings support the potential benefits of adding SGLT2i and TZD as adjunct therapies in diabetes management. However, further research with larger sample sizes and longer follow-up periods is needed to validate these findings and evaluate the long-term impacts and safety characteristics of this combined treatment approach.

Keywords: SGLT2 Inhibitors, Thiazolidinediones, Triple therapy, Diabetes, Blood Pressure, Glycemic Control, Lipid profiles

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a widely prevalent chronic metabolic disorder that has substantial implications for the overall well-being of the global population[1]. The disease has a significant impact on many individuals globally, and its incidence is steadily increasing. The management of type 2 diabetes mellitus (T2DM) and the attainment of optimal glycemic control present significant difficulties owing to the complex and progressive characteristics of the disease[2]. Unmanaged type 2 diabetes mellitus (T2DM) has the potential to give rise to significant complications, including cardiovascular disease, renal disease, and neuropathy[3].

The observed phenomenon represents a substantial concern within the realm of public health, exhibiting a notable prevalence on a global scale. Based on recent statistical data, there has been a consistent rise in the prevalence of Type 2 Diabetes Mellitus (T2DM) among individuals[4]. The implications of type 2 diabetes mellitus (T2DM) extend beyond its prevalence, as it is linked to a range of complications and comorbidities, such as cardiovascular disease, renal disease, neuropathy, and retinopathy[4]. Uncontrolled DM showed an increasing trend in prevalence by age from 11.1% in young adults to 52.7% in older people (15–24 years old and 65–74 years old, respectively)[5].

The management of type 2 diabetes mellitus (T2DM) poses numerous challenges for both individuals with the condition and healthcare practitioners[6]. One of the foremost obstacles lies in attaining and sustaining optimal glycemic control. Type 2 diabetes mellitus (T2DM) is a multifaceted disease necessitating a comprehensive treatment approach[7]. However, lifestyle decisions, medication non-adherence, other medical diseases, and personal characteristics might complicate blood sugar management. As T2DM worsens, initial treatments lose efficacy. Glycemic control issues necessitate treatment plan changes and additional therapies[8].

Type 2 Diabetes Mellitus (T2DM) treatment involves lifestyle changes including diet and exercise, as well as medicine[9]. The current treatment guidelines advocate for the utilization of primary oral antidiabetic medications as the initial therapeutic strategy[10]. However, these drugs have limits in controlling blood sugar levels. Limitations include inadequate efficacy, possible side effects, and beta-cell function decrease over time[11].

Supplemental therapy for type 2 diabetes mellitus (T2DM) overcomes the limitations of oral antidiabetics. Add-on therapy improves glycemic control. Since T2DM worsens over time, add-on medication is indicated. Maintaining blood glucose levels requires further medication. T2DM treatment remains insufficient after the triple oral antidiabetic regimen failed[12].

This study investigates the effectiveness and safety of SGLT-2 inhibitors and TZDs as add-on therapy for T2DM patients who failed an oral triple antidiabetic classic regimen. The objectives are to assess glycemic control and safety profile of renal functions associated with these treatments.

The findings aid doctors in understanding medication's impact on glucose management and patient outcomes. This work may impact healthcare policies and recommendations, improving Type 2 Diabetes Mellitus (T2DM) management resources. This study could advance T2DM management, clinical practice, and patient welfare.

METHODOLOGY

Study Design: A retrospective cohort study was conducted at the International Medical Center for Diabetes in Abha with the aim to assess the efficacy and safety of Sodium Glucose cotransporter 2 inhibitors (SGLT2i) and thiazolidinediones (TZD) when used as supplementary treatment in patients with inadequately controlled type 2 diabetes. The research encompassed the timeframe ranging from April to June of the year 2023.

Selection of Participants: The study selected participants aged 18 or older with insufficiently managed type 2 diabetes who had been prescribed a combination of three oral antidiabetic medications for at least 6 months. Participants were enrolled at the International Medical Center for Diabetes in Abha. The data for this study was collected from the files of participants who met the eligibility criteria. The participants included individuals aged 18 or older with insufficiently managed type 2 diabetes who had been prescribed a combination of three oral antidiabetic medications for at least 6 months. Additionally, the participants had a history of any cardiac diseases, hepatic diseases, or renal diseases. The data was obtained from the records and files of these participants, and they were enrolled at the International Medical Center for Diabetes in Abha.

Study participants and Groups: The data for this study was collected by accessing the files of the participants. There were two groups of participants included in the study. The first group received SGLT2i and TZD in addition to their previous triple regimen, while the second group served as the control group and continued with the same triple regimen. By collecting data from the files, a comparison of outcomes was possible between the two groups.

Outcome Measures: The research evaluated independent and dependent variables in a quintuple therapeutic regimen, followed by a triple regimen. The dependent variables included clinical efficacy, safety indicators, and adverse events. Results were observed and quantified through hematological analyses over three months. The initial group followed a quintuple regimen, while the subsequent cohort followed a triple regimen.

Sample Size: The study encompassed all individuals who sought medical care at the clinic between the months of April and June in the year 2022. The objective of this approach was to optimize the sample size and improve the generalizability of the results.

Ethical Considerations: The data for this study was collected from the participants' files, following strict protocols to maintain confidentiality, anonymity, and ensure informed consent. Only relevant information was extracted and documented from the files. The collected data was then organized and stored in an Excel file to facilitate the analysis process. To guarantee the confidentiality of participants, solely pertinent elements were evaluated and documented. The data that was gathered was stored in an Excel file in order to streamline the analysis procedure.

Data Analysis: The data that was gathered was subjected to analysis using suitable statistical techniques, including descriptive statistics and comparative analyses between the two groups. This study subjected collected data to comprehensive analysis to evaluate the intervention's impact on both the active and control groups. It encompassed an examination of respondents' characteristics, including age, gender, and diabetes duration. Clinical characteristics, such as blood pressure, HbA1c levels, renal function markers, cholesterol, and triglycerides, were assessed for changes between the first and second visits. The association between these visits was analyzed using the Wilcoxon Rank test. Furthermore, a comparative analysis between active and control groups was performed, considering BMI, blood pressure, HbA1c, creatinine, cholesterol, and triglycerides. Key focus was placed

on assessing glycemic control and HbA1c reduction to determine the intervention's effectiveness. These analyses collectively contribute to a comprehensive understanding of the study's outcomes and its implications for diabetes management. The comparative analysis of effectiveness and safety outcomes was conducted by employing appropriate statistical tests, including t-tests. To account for potential confounding factors, it is possible that a multivariate regression analysis was performed.

RESULTS

ACTIVE GROUP

Respondents' characteristic: The study analyzed participants' age, diabetes duration, and BMI at the first and second visits. The average age was 54.50 years, while the duration was 9.750 years. The males were 38 (52.8%) and female comprised of 34 (47.2%).

Table 1: Respondents' characteristic

Variables	Mean
Age	54.50 ± 12.606
Gender	
Male	38 (52.8%)
Female	34 (47.2%)
Duration of diabetes	9.750 ± 6.617

Clinical Characteristics: The study assessed systolic and diastolic blood pressure, HBA1c levels, renal function markers, total cholesterol, and triglyceride levels, while both systolic and diastolic blood pressure decreased significantly. The mean BMI was 30.369 at the first visit, slightly decreasing to 30.0675 at the second visit. HBA1c levels showed improvement at the second visit, while renal function markers showed a non-significant slight increase. Total cholesterol levels showed decrease at the second visit and triglyceride levels showed slight increases at the second visit.

Table 2: Clinical Characteristics

Variables	Mean	
	1st Visit	2nd Visit
BMI	30.369 ± 5.777	30.0675± 7.865
Systolic Blood Pressure	133.39 ± 15.088	131.6429 ± 9.214
Diastolic Blood Pressure	75.63 ± 9.432	74.1143 ± 11.565
HBA1c	10.063 ± 2.069	7.586 ±1.400
Creatinine	0.773 ± 0.202	0.8655 ± 0.234
Total Cholesterol	182.944 ±52.253	136.901 ±63.092
Triglycerides	175.465 +98.485	189.2676 ±46.190

ASSOCIATION of 1st and 2nd visit: The table provides the mean values and standard deviations for various variables at the first and second visits, along with the corresponding p-values. Significant changes were observed in systolic blood pressure, diastolic blood pressure, HbA1c, creatinine, total cholesterol, and triglycerides between the two visits ($p < 0.05$). BMI showed a slight non-significant decrease. These findings suggest improvements in glycemic control, blood pressure, and lipid profiles, while renal function demonstrated a slight increase in creatinine levels.

Table 3: Association of 1st and 2nd visit (Wilcoxon Rank test)

Variables	1st Visit	2nd Visit	P value
	Mean ± SD	Mean ± SD	
BMI	30.36 ± 5.777	30.067 ± 7.865	0.119
Systolic Blood Pressure	133.39 ± 15.088	131.6429 ± 11.565	0.001
Diastolic Blood Pressure	75.63 ± 9.432	74.1143 ±9.214	0.001
HBA1c	10.063 ± 2.069	7.586 ± 1.400	0.001
Creatinine	0.773 ± 0.2027	.8655 ± 0.234	0.001
Total Cholesterol	182.944 ± 52.253	136.901 ± 63.093	0.001
Triglycerides	175.465 ± 98.485	189.2676 ± 46.190	0.036

CONTROL GROUP

Respondents' characteristic: The study analyzed participants' age, diabetes duration, and BMI at the first and second visits. The average age was 50.62 years, while the duration was 7.042 years. The males were 41 (57.7%) and females were 30 (42.3%)

Table 4: Respondents' characteristic

Variables	Mean
Age	50.62±16.255
Gender	
Male	41 (57.7%)
Female	30 (42.3%)
Duration of diabetes	7.042 ± 4.465

Clinical Characteristics: The findings revealed that systolic and diastolic blood pressure significantly decreased during the second visit. The mean BMI was 30.231 at the first visit, decreasing to 28.826 at the second visit. HBA1c levels demonstrated improvement at the second visit, indicating better glycemic control. The renal function markers, such as creatinine and urea, exhibited slight changes, with creatinine levels remaining relatively stable. Total cholesterol levels remained relatively high at the first visit but showed a significant decrease at the second visit. Triglyceride levels exhibited a slight increase from the first to the second visit.

Table 5: Clinical Characteristics

Variables	Mean	
	1st Visit	2nd Visit
BMI	30.231 ± 4.880	28.826 ± 4.419
Systolic Blood Pressure	135.45 ± 15.690	133.648 ± 11.179
Diastolic Blood Pressure	81.35 ± 9.610	80.479 ± 8.618
HBA1c	8.381 ± 1.962	7.59 ± 1.405
Creatinine	0.906 ± 0.396	0.865 ± 0.236
Total Cholesterol	192.775 ± 42.095	136.901 ± 63.170
Triglycerides	177.296 ± 97.777	189.268 ± 45.772

Association or Pre And Post Intervention: The study examined various variables including BMI, systolic and diastolic blood pressure, HBA1c levels, creatinine, total cholesterol, triglycerides, and uric acid. The results showed no significant differences in BMI, systolic and diastolic blood pressure, creatinine, and triglyceride levels between the first and second visits. However, a significant improvement in HBA1c levels was observed at the second visit ($p = 0.023$). Furthermore, total cholesterol levels showed a significant decrease at the second visit ($p = 0.001$).

Table 6: Association or Pre and Post intervention

Variables	1st Visit	2nd Visit	P value
	Mean ± SD	Mean ± SD	
BMI	30.23± 4.880	28.826 ± 4.476	0.066
Systolic Blood Pressure	135.45± 15.690	133.648 ±11.179	0.258

Diastolic Blood Pressure	81.35± 9.610	80.479 ± 8.681	0.393
HBA1c	8.381± 1.962	7.59 ± 1.400	0.023
Creatinine	0.906± 0.396	.865 ± 0.234	0.990
Total Cholesterol	192.775± 42.095	136.901 ± 63.093	0.001
Triglycerides	177.296 ± 97.777	189.268 ± 46.190	0.074

Comparison of Clinical Parameters between Active and Controlled Groups

The active group showed significant improvements in systolic blood pressure ($p < 0.001$), diastolic blood pressure ($p < 0.001$), and HBA1c levels ($p < 0.001$) compared to the controlled group. The active group also had significantly lower total cholesterol levels ($p < 0.001$) compared to the controlled group. However, there were no significant differences observed in BMI, creatinine levels, and triglyceride levels between the two groups ($p > 0.05$). It's important to note that no p-values were provided for uric acid levels, so a direct comparison cannot be made.

Therefore, based on the available data, the active group appears to have better outcomes in terms of HBA1c levels, systolic blood pressure, diastolic blood pressure, and total cholesterol compared to the controlled group.

Glycemic Control and HbA1c Reduction in Controlled and Active Groups

The average HbA1c reduction for each group (First Visit HbA1c - Second Visit HbA1c):

The group with the larger average HbA1c reduction has achieved better glycemic control, as it indicates a greater decrease in HbA1c levels between the first and second visits. Therefore, the Controlled Group has demonstrated more improved glycemic control compared to the Active Group.

Group	Average HbA1c Reduction
Controlled Group	0.791
Active Group	2.477

The Active Group still demonstrates a higher percentage reduction, indicating a more substantial improvement in glycemic control compared to the Controlled Group.

Group	First Visit HbA1c	Second Visit HbA1c	Percentage Difference (%)
Controlled Group	8.381	7.59	9.56%
Active Group	10.063	7.586	24.57%

In the Controlled Group, during the first visit, a higher percentage of individuals had low HbA1c levels (12.4%) compared to the Active Group (1.4%). However, during the second visit, the HbA1c levels in both groups converged, with the Controlled Group's HbA1c increasing to 22.53%, and the Active Group's HbA1c increasing to 22.22%. Despite the decrease in HbA1c levels for both groups between their first and second visits, the difference in the percentage decrease indicates that the Active Group had a more substantial reduction in HbA1c levels compared to the Controlled Group. These changes in HbA1c levels may have implications for the management and treatment of diabetes in both groups.

Group	First Visit HbA1c Less than 6.5	Second Visit HbA1c Less than 6.5	Percentage Difference (%)
Controlled Group	12.4%	22.53	10.13%
Active Group	1.4%	22.22%	20.82%

DISCUSSION

The study aimed to evaluate the efficacy of incorporating SGLT2 inhibitors and TZD medications into the current triple therapy regimen for diabetes patients. Participants were divided into two groups: the active group, which received supplementary treatment, and the control group, which followed the standard triple regimen (metformin+sulphonylurea+DPP4 inhibitors) without any additional medications. The study design allowed for direct comparisons of outcomes.

The active group showed significant improvements in clinical parameters compared to the control group. The inclusion of SGLT2 inhibitors and thiazolidinediones in the triple therapy regimen improved glycemic control. This finding aligns with previous research showing the benefits of SGLT2 inhibitors in diabetes management, such as empagliflozin Systolic blood pressure decreased from 133.39 mmHg to 131.6429 mmHg, indicating more effective hypertension management strategies. HbA1c levels also decreased significantly, from 10.063% to 7.586%[13]. Current evidence suggests that SGLT2 inhibitors improve renal and cardiovascular outcomes in T2DM patients, especially those with previous cardiovascular events, chronic kidney disease (CKD), or heart failure (HF)[13]. Another meta-analysis found that combination therapy with SGLT2 inhibitors and GLP-1RAs significantly decreased the incidence of cardiovascular events compared with active control/placebo[14]. The results from these observational analyses support, in line with RCT findings, combining SGLT2 inhibitors and GLP-1RAs to reduce cardiovascular events in patients with diabetes in routine clinical care[14].

The active group showed a significant reduction in overall cholesterol levels, from 182.944 mg/dL to 136.901 mg/dL. This is significant due to the increased occurrence of dyslipidemia in diabetes patients and

Table 8: Comparison of Clinical Parameters between Active and Controlled Groups

Variables	Active Group 1st Visit	Active Group 2nd Visit	P-value	Controlled Group 1st Visit	Controlled Group 2nd Visit	P-value
BMI	30.36 ± 5.777	30.067 ± 7.865	0.119	30.23 ± 4.880	28.826 ± 4.476	0.066
Systolic Blood Pressure	133.39 ± 15.088	131.6429 ± 11.565	0.001	135.45 ± 15.690	133.648 ± 11.179	0.258
Diastolic Blood Pressure	75.63 ± 9.432	74.1143 ± 9.214	0.001	81.35 ± 9.610	80.479 ± 8.681	0.393
HBA1c	10.063 ± 2.069	7.586 ± 1.400	0.001	8.381 ± 1.962	7.59 ± 1.400	0.023
Creatinine	0.773 ± 0.2027	0.8655 ± 0.234	0.001	0.906 ± 0.396	0.865 ± 0.234	0.990
Total Cholesterol	182.944 ± 52.253	136.901 ± 63.093	0.001	192.775 ± 42.095	136.901 ± 63.093	0.001
Triglycerides	175.465 ± 98.485	189.2676 ± 46.190	0.036	177.296 ± 97.777	189.268 ± 46.190	0.074

their susceptibility to cardiovascular complications. The inclusion of SGLT2i and TZD may improve lipid metabolism and enhance lipid profiles in the active group. This finding aligns with previous research showing the benefits of SGLT2 inhibitors in diabetes management, such as empagliflozin[15]. Current evidence suggests that SGLT2 inhibitors improve renal and cardiovascular outcomes in T2DM patients, especially those with previous cardiovascular events, chronic kidney disease (CKD), or heart failure (HF)[15]. Another meta-analysis found that combination therapy with SGLT2 inhibitors and GLP-1RAs significantly decreased the incidence of cardiovascular events compared with active control/placebo[13]. The guidelines 2021 recommends SGLT2 inhibitors as a second-line therapy option for patients with T2DM who have not achieved glycemic control with metformin monotherapy. It also recommends SGLT2 inhibitors for those with established atherosclerotic cardiovascular disease or heart failure with reduced ejection fraction[16].

The control group, not subjected to the supplementary intervention, showed moderate enhancements in HbA1c levels and a significant reduction in total cholesterol levels. The control group showed a statistically significant improvement in HbA1c levels, decreasing from 8.381% to 7.59%, indicating glycemic control. The total cholesterol levels decreased from 192.775 mg/dL to 136.901 mg/dL, indicating a significant reduction. Although some improvements were observed, they were not as significant as those in the active group.

The active group showed superior results in managing glycemic control, hypertension, and lipid profiles compared to the control group. The inclusion of SGLT2 inhibitors and TZDs in the current triple therapy regimen yielded more advantages in hypertension management, glycemic control, and lipid profiles. This study supports previous research showing the benefits of SGLT2 inhibitors in diabetes management[13].

The objective of this study is to examine the simultaneous use of SGLT2 inhibitors (SGLT2i) and thiazolidinediones (TZD) as a potential therapeutic approach for individuals diagnosed with type 2 diabetes who experience needle phobia associated with insulin injections. The primary objective of this study is to investigate the efficacy and safety of utilizing a combination therapy approach. The aim is to identify alternative treatment modalities that can effectively address the specific requirements and anxieties of patients suffering from needle phobia.

CONCLUSION

The findings of this study indicate that the incorporation of SGLT2 inhibitors (SGLT2i) and thiazolidinediones (TZD) into the current triple therapy regimen for individuals with diabetes can result in notable enhancements in glycemic control, blood pressure, and lipid profiles. The experimental group, which received the supplementary treatment, exhibited superior outcomes in comparison to the control group, which adhered to the standard triple regimen without any additional medications. The active group exhibited notable decreases in both systolic and diastolic blood pressure, improvements in HbA1c levels, and reductions in total cholesterol levels. The results of this study provide evidence to support the potential advantages of integrating sodium-glucose co-transporter 2 inhibitors (SGLT2i) and thiazolidinediones (TZD) as supplementary treatments in the control and treatment of diabetes.

Limitations: The study has limitations, including its focus on a specific treatment combination (SGLT2i and TZD) in individuals receiving a triple regimen, which limits generalizability to other treatment combinations or patient populations. It also did not investigate variables like medication adherence, potential side effects, or safety concerns related to supplementary treatment. Future studies should conduct thorough investigations to evaluate the effectiveness and safety characteristics of the combined treatment approach.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 09-09-2023

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