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ORIGINAL ARTICLE

Comparison of metformin plus modified release gliciazide with metformin plus sitagliptin for treatment of diabetes mellitus.

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ABSTRACT… Objective: To compare the efficacy of metformin plus modified-release gliclazide versus metformin plus sitagliptin in reducing HbA1c levels in patients with type II diabetes mellitus. **Study Design:** Randomized Controlled Trial. **Period:** August'2021 to January'2022. **Setting:** Medical Outdoor, Allied Hospital Faisalabad. **Methods:** Total 200 patients with type II diabetes mellitus of either gender of age 30-60 years were selected. Group A patients took combination of metformin (1000 mg/day) and modified release gliclazide (60 mg/day) for 12 weeks. Group B patients took combination of metformin (1000 mg/day) and sitagliption (100 mg/day) for 12 weeks. **Results:** The mean age of patients in group A was 43.43 ± 9.76 years and in group B was 45.83 ± 7.86 years. Out of 200 patients, 86 (43.0%) were males and 114 (57.0%) were females with male to female ratio of 1:1.3. In my study, mean HbA1c after 12 weeks of treatment with combination of metformin and Gliclazide was 6.53% ± 0.18 and with combination of metformin and sitagliptin it was 6.40% ± 0.10 (p-value = 0.0001). **Conclusion:** This study concluded that thecombination of Metformin and Sitagliptan is better than combination of Metformin and for modified release Gliclazid treatment of type II diabetes mellitus in terms of mean HbA1c.

Key words: HbA1c, Sitagliptin, Type 2 Diabetes.

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INTRODUCTION

A group of metabolic illnesses that are collectively referred to as diabetes can be characterized by hyperglycemia that is brought on by abnormalities in either the function or synthesis of insulin, or both.[1,2] Globally, the prevalence of diabetes mellitus ranges from 10% to 14%.[3] One of the defining characteristics of diabetes mellitus type 2, sometimes referred to as noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is the presence of high blood glucose levels in the context of insulin resistance and relative insulin deficiency. It is possible for there to be no insulin at all if the pancreatic islet cells are taken out of the equation.[2]

Sulfonylureas, including modified-release (MR) gliclazide, and DPP-4 inhibitors, such as sitagliptin, are commonly employed as second-line treatments. Both improve glycaemic control, although they do so in different ways, have different risks of hypoglycemia, affect weight differently, and cost different amounts. In ordinary clinical practice, comparing the effectiveness and safety of metformin + gliclazide MR with metformin + sitagliptin can help find the best treatment for people with T2DM. When it comes to the treatment of type 2 diabetes mellitus, a comparison of metformin with modified-release gliclazide and metformin plus sitagliptin reveals significant differences in terms of both efficacy and safety profiles: Metformin decreases hepatic glucose production and improves insulin sensitivity; gliclazide stimulates insulin secretion as a sulfonylurea; and sitagliptin is a DPP-4 inhibitor that increases glucose-dependent insulin secretion. Both combinations are aimed at glycaemic control; however, they differ in the mechanisms by which they accomplish this. It has been demonstrated through clinical research that the combination of gliclazide MR and metformin is more effective in lowering HbA1c levels than the combination of sitagliptin and metformin.[4] Furthermore, the combination of these two medications has a similar impact that lasts longer and patients continue to take it.

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Sitagliptin, a DPP-4 inhibitor, lowers blood glucose by preserving incretin hormones and enhancing insulin secretion. It offers advantages such as no weight gain, low risk of hypoglycemia, and may improve islet cell function by promoting proliferation, reducing apoptosis, and suppressing glucagon secretion. Furthermore, sitagliptin increases islet cell proliferation, decreases cell apoptosis, and reduces glucagon secretion in vitro.[5] In a study, mean HbA1c after 12 weeks of treatment with combination of metformin and Gliclazide was 6.5% ± 0.15 (6.4-7) and with combination of metformin and sitagliptin it was 6.4% ± 0.175 (6.3 -7).[6]

When compared to DPP-4 inhibitors like as sitagliptin, sulfonylureas have the potential to pose a higher risk of hypoglycemia. However, gliclazide MR has been around for a longer period of time and has proven to be successful in lowering blood glucose levels. The choice between these combinations is frequently determined by patient-specific factors such as glycaemic objectives, the risk of hypoglycemia, considerations regarding weight, and ability to tolerate the medication.[7] The progressive metabolic disease known as type 2 diabetes mellitus (T2DM) is steadily receiving international attention as a possible pandemic.

The International Diabetes Federation (IDF) has projected that by the year 2040, the number of people who have diabetes will have increased to 642 million, which is equivalent to one in ten adults. As of 2015, the number of people who have diabetes is 415 million, which is equivalent to one in eleven adults.[8] There is still a lack of direct comparative data between these two regimens, particularly in conditions that are representative of the actual world. In patients with type 2 diabetes who are not effectively managed by metformin monotherapy, the purpose of this study is to evaluate the effectiveness, safety, and tolerability of metformin plus modified-release gliclazide in comparison to metformin plus sitagliptin. This study aims to compare the efficacy of two metformin-based dual-combination therapies for managing type II diabetes mellitus in a local setting, where limited local data currently exists.

METHODS

The primary objective is to assess the mean HbA1c levels after 12 weeks of treatment with either metformin plus modified-release gliclazide or metformin plus sitagliptin. The hypothesis posits that the metformin-sitagliptin combination will yield better glycemic control (lower HbA1c) than the metformin-gliclazide combination. Type II diabetes mellitus is operationally defined as fasting blood sugar ≥126 mg/dL or random blood sugar ≥200 mg/dL, while HbA1c is measured via hospital pathology laboratory tests after the 12-week intervention.

The study is designed as a randomized controlled trial conducted at the Medical Outdoor Department of Allied Hospital, Faisalabad after the approval of CPSP and Institutional Ethical Review Board (Reference.No.869, Date: 13-07-2021). Using the WHO sample size calculator for two means, a total of 200 participants (100 per group) were determined, with an anticipated mean HbA1c of 6.5%, a test value of 6.4%, a pooled standard deviation of 0.16, a 5% significance level, and 80% power. Non-probability consecutive sampling was employed for recruitment.

Inclusion criteria consist of patients aged 30 to 60 years with HbA1c values between 6.5% and 11%, currently administered metformin at a dosage of 1000 mg/day, and with a BMI of less than 40 kg/m^2. important cardiovascular events, increased liver enzymes (AST/ALT >2.5× upper limit), elevated serum creatinine (men: >1.5 mg/dL; women: >1.4 mg/dL), systemic corticosteroid use in the prior 12 weeks, insulin therapy, or pregnancy are all important reasons why someone might not be included. After getting permission from the ethics board, eligible OPD patients gave their informed consent and were randomly put into either Group A (metformin + gliclazide MR 60 mg/day) or Group B (metformin + sitagliptin 100 mg/day). At 12 weeks, HbA1c was tested, and follow-ups were done by phone.

SPSS Version 23 was used to analyse the data. The mean ± SD was used to report age, disease duration, and HbA1c, while frequencies and percentages were used to describe the gender distribution. An independent samples t-test was conducted to evaluate post-treatment HbA1c levels between groups, incorporating stratification for effect modifiers such as age, disease duration, and

gender, followed by post-stratification t-tests. A p-value of less than or equal to 0.05 was considered statistically significant. This study aims to inform local treatment decisions by assessing the optimal dual-therapy approach for glycaemic management in type II diabetes.

RESULTS

There were 200 patients with type II diabetes mellitus in the study, and they were randomly put into two therapy groups. Group A got metformin and modified-release gliclazide, whereas Group B got metformin and sitagliptin. The average age of all the people who took part was 44.66 ± 8.65 years. Group A's average age was 43.43 ± 9.76 years, while Group B's average age was 45.83 ± 7.86 years. Of the 200 people who took part, 86 were men (43%) and 114 were women (57%). This means that there were about 1.3 men for every woman. The average weight was 75.63 ± 8.35 kg, the average height was 165.86 ± 14.76 cm, and the average body mass index (BMI) was 29.12 ± 3.31 kg/m^2. The average length of time that people had diabetes was 9.87 ± 3.84 years. 45% of people had it for less than 10 years, while 55% had it for more than 10 years.

After 12 weeks of treatment, Group B (metformin + sitagliptin) showed much improved glycaemic control, with a mean HbA1c of 6.40 ± 0.10%, compared to 6.53 ± 0.18% in Group A (metformin + gliclazide). The p-value of 0.0001 was very significant.

Stratified analysis showed that all subgroups had the same patterns. When divided by age, patients aged 30–45 years had HbA1c levels of 6.55 ± 0.17% in Group A and 6.40 ± 0.11% in Group B. Those aged 46–60 years had values of 6.51 ± 0.20% and 6.39 ± 0.11%, respectively. Both groups showed statistically significant differences (p = 0.0001). When looking at the data by gender, it was found that men in Group A had a mean HbA1c of 6.53 ± 0.17% while women in Group B had a mean HbA1c of 6.54 ± 0.19%. Again, both comparisons were statistically significant (p = 0.0001). Similarly, patients with a duration of diabetes ≤10 years had mean HbA1c values of 6.54 ± 0.16% in Group A and 6.39 ± 0.08% in Group B. Among those with >10 years duration, the values were 6.53 ± 0.20% and 6.41 ± 0.12%, respectively (p = 0.0001 for both).

These results collectively demonstrate that the combination of metformin and sitagliptin consistently leads to greater reductions in HbA1c levels compared to metformin and gliclazide MR, regardless of patient age, gender, or duration of diabetes.

TABLE-I

Baseline characteristics of study participants (N = 200)

Variable	Group A (n = 100)	Group B (n = 100)	Total (n = 200)
Age (years)	43.43 ± 9.76	45.83 ± 7.86	44.66 ± 8.65
Gender (Male/Female)	41 / 59	45 / 55	86 / 114 (M:F = 1:1.3)
BMI (kg/m^2)	-	-	29.12 ± 3.31
Height (cm)	-	-	165.86 ± 14.76
Weight (kg)	-	-	75.63 ± 8.35
Duration of Diabetes (years)	9.81 ± 3.87	9.95 ± 3.97	9.87 ± 3.84

TABLE-II

HBA1C after 12 weeks of treatment

Group	Mean HbA1c (%) ± SD	P-Value
Group A (Metformin + Gliclazide MR)	6.53 ± 0.18	
Group B (Metformin + Sitagliptin)	6.40 ± 0.10	0.0001

TABLE-III

Stratification of HBA1C by age, gender, and duration of diabetes

Stratification Variable	Category	Group A HbA1c (Mean ± SD)	Group B HbA1c (Mean ± SD)	P-Value
Age (years)	30–45	6.55 ± 0.17	6.40 ± 0.11	0.0001
	46–60	6.51 ± 0.20	6.39 ± 0.11	0.0001
Gender	Male	6.53 ± 0.17	6.42 ± 0.11	0.0001
	Female	6.54 ± 0.19	6.38 ± 0.10	0.0001
Duration of Diabetes	≤10 years	6.54 ± 0.16	6.39 ± 0.08	0.0001
	>10 years	6.53 ± 0.20	6.41 ± 0.12	0.0001

DISCUSSION

The chronic metabolic condition known as type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, increasing β-cell dysfunction, and impaired glucose metabolism, which ultimately results in prolonged hyperglycemia. There is a continuing increase in the global burden of diabetes, with estimates showing that more than 530 million adults are currently affected by the condition. It is anticipated that this figure will approach 780 million by the year 2045. It is still essential to maintain optimal glycemic control as the foundation of diabetes therapy in order to lessen the likelihood of developing microvascular and macrovascular problems.[9]

Due to its efficacy, safety profile, cardiovascular advantages, and weight-neutral effect, metformin is regarded to be the pharmacologic agent of first-line treatment.

In 2014, it was projected that 9% of individuals worldwide had diabetes, with 90% of these instances being type 2 diabetes (T2D). With fasting plasma glucose (FPG) alone, the probable incidence of diabetes in individuals aged ≥30 years in Korea is 10.5%, and with both FPG and HbA1c, it is 12.4%, according to the Korea National Health and Nutrition Examination Survey 2011.[10]

In 30% to 50% of patients, diabetes is closely linked to both microvascular and macrovascular problems that cause damage to organs and tissues, and the risk of these complications is substantially correlated with prior hyperglycemia.[11] Even if subsequent therapy is less rigorous, diabetes has a positive momentum that might last for 10 years or more.[12] The new paradigm of therapy for T2D that aims to reach glycemic objectives early is supported by these recent findings individuals.[13]

When the initial HbA1c levels are greater than 7.5% (58 mmol/mol), the American Association of Clinical Endocrinologists (AACE) treatment algorithm recommends the early use of mixed therapy with metformin. This is because it has been demonstrated that reaching HbA1c levels below 7.0% (53 mmol/mol) is essential for achieving a prolonged reduction in microvascular complications, and possibly macrovascular complications as well. The American Diabetes Association (ADA) 2015 Standards of Medical Care in Diabetes recommend that patients with a high baseline HbA1c (≥9.0% [75 mmol/mol]) begin treatment with a combination of two non-insulin oral antihyperglycemic agents (AHAs). This is due to the fact that metformin monotherapy is not likely to assist these patients in reaching their target HbA1c.[14] As a result, individuals with type 2 diabetes may benefit greatly from the early commencement of combination treatment using AHAs that function via distinctively diverse pathways.

Prior research evaluating the safety and effectiveness of sitagliptin and metformin combination treatment in the Korean population has indicated that this dual medication is both effective and well-tolerated. According to a recent study, drug-naïve Korean patients who received metformin-based combination therapies with either sitagliptin, pioglitazone, or a sulfonylurea (glimepiride or gliclazide modified release) showed comparable glycemic effectiveness across a broad range of baseline HbA1c levels.[15] In another trial, glycemic control significantly improved when sitagliptin 100

mg/day was administered to Korean patients who had previously received combination therapy (dual or triple combination therapies with metformin). The incidence of hypoglycemic episodes actually dropped in the group that went from glimepiride to sitagliptin, indicating that patients with recurrent fasting hypoglycemia may want to think about doing so.[16]

The benefits of combination therapy were evaluated using a meta-analysis of 15 randomised clinical studies, which included the participation of about 7,000 persons who were diagnosed with type 2 diabetes respectively. The average age range in this study was 48.4–62.7 years, the average baseline HbA1c was 7.2–9.9%, and the average duration of diabetes was 1.6–4.1 years. All of these values were representative of the population. In these research, metformin was administered in conjunction with a number of other drugs, including thiazolidinediones (TZDs), insulin secretagogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium glucose transporterase (SGLT-2) inhibitors. In contrast to metformin monotherapy, combined therapy was found to result in significant reductions in HbA1c levels. As a result of the combination treatment, the FPG was reduced, and the HbA1c goal level accomplishment was increased (HbA1c <7%).[17]

According to the findings of this study, the combination of Metformin and Sitagliptan is superior to the combination of Metformin and for modified release Gliclazid treatment of type II diabetes mellitus in terms of the mean HbA1c. Therefore, in order to lessen the morbidity associated with type II diabetes mellitus, we suggest that metformin and sitagliptan be utilised as the primary medication for regulating blood sugar levels in patients with this condition.

CONCLUSION

This study concluded that the combination of Metformin and Sitagliptan is better than combination of Metformin and for modified release Gliclazid treatment of type II diabetes mellitus in terms of mean HbA1c. So, we recommend that Metformin and Sitagliptan should be used as a primary treatment for controlling blood sugar in type II diabetes mellitus in order to reduce their morbidity.

LIMITATIONS

It was conducted at a single tertiary care hospital. Secondly, the follow-up period was limited, which does not allow for evaluation of long-term glycemic control, medication adherence, or sustainability of therapeutic effects. The use of non-probability consecutive sampling could have introduced selection bias. Additionally, the study did not mention any blinding of participants or investigators, increasing the risk of performance and detection bias. The focus was solely on HbA1c levels as the primary outcome, without consideration of other clinically significant parameters such as incidence of hypoglycemia, changes in body weight, or patient-reported outcomes. Furthermore, the safety and tolerability of the drug combinations were not assessed, which is essential for making informed treatment decisions in routine clinical practice.

RECOMMENDATIONS

Incorporating blinding in study design would reduce potential bias and improve the reliability of results. It is also recommended that future studies include additional outcome measures such as the frequency of hypoglycemic episodes, changes in body weight, patient satisfaction, and adherence to therapy. Monitoring adverse drug reactions and overall tolerability should be an integral part of study protocols. Lastly, a cost-effectiveness analysis comparing the two treatment combinations would provide valuable insights for healthcare providers and policy-makers, especially in resource-constrained settings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Numra Shabbir:** Data collection, analysis.
2	**Saba Gulnaz:** Data collection, paper writing.
3	**Madeeha Qamar:** Data analysis.
4	**Salman Azhar:** Discussion writing.
5	**Wasif Baig:** Review of manuscript.
6	**Muhammad Afham Shahid:** Data analysis.