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A STUDY ON SAFETY AND EFFICACY OF PIOGLITAZONE VERSUS VOGLIBOSE ADJUNCTS TO GLIMEPERIDE AND METFORMIN IN TYPE 2 DIABETES MELLITUS: A CLINICAL COMPARISION

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ABSTRACT

Background: Type-2 Diabetes Mellitus (T2DM) is a progressive metabolic disorder requiring combination therapy for optimal glycemic control. Glimeperide and Metformin are commonly prescribed as first line agent: however, additional agents like Voglibose and Pioglitazone are often needed. **Aims and Objectives:** To evaluate the safety and efficacy of voglibose versus pioglitazone adjuncts to glimepiride and metformin in type-2 diabetes mellitus; A clinical comparison. **Methodology:** This was the prospective observational study was conducted over 6 months in sree shakti nursing home yemmiganur. A total of 120 patients with T2DM were enrolled and divided into two groups. Group A received Voglibose, while Group B received Pioglitazone, in addition to their existing therapy. The primary endpoints were changes in fasting blood glucose (FBG), postprandial blood glucose (PPBG), and HBA1c over 12 weeks. Secondary outcomes included assessment of adverse effects. **Results:** Both Voglibose and Pioglitazone significantly reduced FBG, PPBG and HBA1c levels compared to baseline (p lessthan 0.05). Voglibose showed superior control of postprandial hyperglycemia, while Pioglitazone demonstrated a greater reduction in HBA1c. However, VPioglitazone was associated with Headache, Edema in some patients, whereas Voglibose was associated with flatulence and abdominal discomfort. **Conclusion:** Though pioglitazone and voglibose were equally effective, pioglitazone showed better results in controlling glycaemic profile (FBG, PPBG) and in lowering HbA1c as compared to voglibose. moreover, pioglitazone had minimal side effects as compared to voglibose.

KEYWORDS: Type 2 Diabetes Mellitus, Pioglitazone, Voglibose, Glimeperide, Metformin.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia (high blood glucose levels), resulting from defects in insulin secretion, insulin action, or both. It is one of the most prevalent non- communicable diseases worldwide and poses a major public health challenge due to its increasing incidence and associated complications.

It has many sub classifications, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes.

Type 1 and 2 DM are the main subtypes, each with different pathophysiology presentation, and management.

1 Type Diabetes Mellitus (T1DM)
Cause: Autoimmune destruction of pancreatic beta cells.

Onset: Usually in childhood or adolescence, but can occur at any age

Features: Absolute insulin deficiency requires lifelong insulin therapy.

Subtypes
Type 1A (autoimmune) Type 1B (idiopathic)
2. Type 2 Diabetes Mellitus (T2DM)
Cause: Insulin resistance and relative insulin deficiency.
Onset: Usually in adults, often associated with obesity.
Features: Managed with lifestyle changes, oral medications, and sometimes insulin.

3. Gestational Diabetes Mellitus (GDM)
Cause: Glucose intolerance first recognized during pregnancy.
Features: Usually resolves after delivery but increases risk of developing T2DM later in life.

4. Other Specific Types (Secondary Diabetes)
These are due to specific causes
- **Genetic defects of beta-cell function** (e.g., MODY – Maturity Onset Diabetes of the Young)
- **Genetic defects in insulin action**
- **Diseases of the exocrine pancreas** (e.g., pancreatitis, cystic fibrosis)
- **Endocrinopathies** (e.g., Cushing's syndrome, acromegaly) Drug or **chemical-induced** (e.g., steroids, thiazides) **Infections** (e.g., congenital rubella, CMV)
- Prediabetes (Intermediate Hyperglycemia):
- Impaired Fasting Glucose (IFG)
- Impaired Glucose Tolerance (IGT)
- Increased risk of developing T2DM.

Etiologic Classification of Diabetes Mellitus
1. **Type 1 diabetes** (beta-cell destruction, usually leading to absolute insulin deficiency)
- Immune mediated
- Idiopathic

2. **Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
3. **Gestational Diabetes mellitus** (GDM)
- Genetic defects of beta -cell function Drug (like steroids)

PATHOGENESIS OF DIABETES MELLITUS
Pathophysiology of type 1 diabetes
In this condition the immune system attacks and destroys the insulin producing beta cells of the pancreas.it termed an autoimmune disease where there are anti insulin or anti-islet cell antibodies present in blood. These cause lymphocytic infiltration and destruction of the pancreas islets.[4]

Pathophysiology of type 2 diabetes
This condition is caused by beta cell deficiency coupled with peripheral insulin resistance.

Peripheral insulin resistance means that although blood levels of insulin are high there is no hypoglycaemia or low blood sugar. This may be due to changes in the insulin receptors that bring about the actions of the insulin.

SIGNS AND SYMPTOMS
1. General
- Fatigue
- Weight loss (especially in Type 1 diabetes)
- Increased thirst (polydipsia)
- Frequent urination (polyuria)
- Increased hunger (polyphagia)

2. Eyes (Ophthalmologic)
- Blurred vision
- Diabetic retinopathy (can lead to vision loss)
- Cataracts

3. Nervous System
- Peripheral neuropathy (tingling, numbness in hands/feet)
- Autonomic neuropathy (e.g., gastroparesis, erectile dysfunction)

4. Skin
- Itching (pruritus)
- Slow wound healing
- Recurrent skin infections (fungal/bacterial)
- Acanthosis nigricans (darkened skin folds)

5. Gastrointestinal
- Gastro paresis (delayed gastric emptying)
- Constipation or diarrhoea

6. Musculoskeletal
- Joint stiffness
- Muscle weakness
- Charcot joint (in severe neuropathy cases)

DIAGNOSIS OF DIABETES
Prediabetes can be diagnosed with any of the following criteria
- Impaired fasting glucose (IFG): FPG 100 mg/dL to 125 mg/dL or
- Impaired glucose tolerance (IGT): 2-h plasma glucose (2-h PG) during 75-g OGTT 140 mg/Dl to 199 mg/dL or
- HbA1c ≥5.7%-6.4%

Diabetes can be diagnosed by
- FPG ≥126 mg/dL or
- FPG ≥126 mg/dL and/or 2-h PG ≥200 mg/dL using 75-g OGTT
- HbA1c≥6.5% or
- Random plasma glucose ≥200 mg/dL in the presence of classical diabetes symptoms.

Asymptomatic individuals with a single abnormal test should have the test repeated to confirm the diagnosis unless the result is unequivocally abnormal.

COMPLICATIONS OF DM

Acute Complications

1. **Hypoglycaemia –** low blood sugar due to excess insulin or missed meals.
2. **Diabetic ketoacidosis (DKA) –** mostly in Type 1 diabetes; due to insulin deficiency.
3. **Hyperosmolar hyperglycaemic state (HHS) –** mostly in Type 2 diabetes; severe hyperglycemia without ketoacidosis.

Chronic complications

Microvascular Complications

1. Diabetic retinopathy – can lead to blindness.
2. Diabetic nephropathy – can cause kidney failure.
3. Diabetic neuropathy – includes peripheral neuropathy, autonomic neuropathy.

COMORBIDITIES OF DIABETES MELLITUS

1. Diabetes mellitus with hypertension

Diabetes mellitus (DM) and hypertension commonly coexist, significantly increasing the risk of cardiovascular, renal, and ocular complications.

Management

- Strict blood glucose and blood pressure.
- Regular monitoring of renal function and cardiovascular status
- Antihypertensive medications like ACE inhibitors, ARBs, CCBs, Diuretics, Beta blockers prefferd in diabetic patients**.**

2. Diabetes mellitus with tuberculosis

Diabetes mellitus increases susceptibility to infections, including TB, due to impaired immunity.

Management

- Anti-TB therapy is the same, monitor for drug interactions-especially rifampicin, which can lower the effectiveness of sulfonylureas and other oral Anti-diabetic agents.

TREATMENT

General Principles

Metformin should be initiated in combination with lifestyle interventions at the time of diagnosis.

1. Maintain support for lifestyle measures throughout
2. Consider each initiation or dose increase of OADs as a trial, monitoring the response through glucose monitoring (FPG, PPG, self-monitoring of Blood glucose [SMBG] or HbA1c) every 2-3 months.
3. Consider CV/heart failure risk, renal/hepatic (NASH) risk while deciding therapy
4. Patient-centric approach: consider cost and benefit risk ratio when choosing OADs
5. Customise therapy focusing on individualised target HbA1c for each patient based on: age, duration of diabetes, comorbidities, cost of therapy, Hypoglycaemia risk, weight gain, durability
6. Consider initiating combination therapy if the HbA1c >1.5 above the targetInitial Therapy
7. Metformin should be initiated in combination with lifestyle interventions at the time of diagnosis unless contra-indicated or not tolerated.
8. If eGFRis between 45-30 mL/min/1.73m2: reduce dose of metformin by 50%; stop metformin if eGFR <30 mL/min/1.73m2
9. monitor renal Function every 3 months
10. Other options: sulfonylurea (or glinides), dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors, or AGIs can be used initially for cases where Metformin is contraindicated or not tolerated
11. In some cases, dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets

Dual therapy

- If glucose control targets are not achieved: Add sulfonylurea or thiazolidinediones (TZDs) or sodium-glucose cotransporter 2 inhibitors (SGLT2) Inhibitor, or DPP-4 inhibitor, or AGI.

Triple therapy

- If glucose targets are not achieved with two agents: start third oral agent-AGI, DPP-4 inhibitor, SGLT2 inhibitor, or TZDs (depending on second-line agent used) or start insulin or glucagon-like peptide 1 (GLP-1) agonists.
- For patients with established atherosclerotic cardiovascular disease (ASCVD), heart failure, diabetic kidney disease (DKD) or in need of weight reduction consider using SGLT2 inhibitors.
- If postprandial hypoglycaemia is the issue AGI, glinides or SGLT2 inhibitors may be considered.
- In elderly patients with increased risk of hypoglycaemia, use a DPP-4 inhibitor as an alternative to sulfonylurea.

Non pharmacology therapy

1. Diet control – Low sugar, high fiber, balanced meals.
2. Exercise – At least 150 mins/week of moderate activity.
3. Weight loss – 5–10% weight reduction helps a lot.
4. Education – Learn self-care and glucose monitoring.
5. No smoking – Reduces heart and blood vessel risks.

METHODOLOGY

Study design: Prospective observational study, Comparative clinical study

Study Site: Sree Shakti Hospital, Yemmiganur

Study Subjects: Sample size is 120 patients (each group 60 subjects), contains two groups i.e,

Group A: (Glimepiride 2mg BD + Pioglitazone 15mg + Metformin Hydrochloride 500mg)

Group B: (Glimepiride 2mg BD + Voglibose 0.2mg +

Metformin Hydrochloride 500mg)
Study period: 6 months

Statistical analysis: MS Excel and t test
INCLUSION CRITERIA

- ✓ Patients diagnosed with type 2 Diabetes mellitus
- ✓ Age group of 30-75 years of either sex
- ✓ Patient with comorbid conditions such as hypertension and tuberculosis

EXCLUSION CRITERIA

- Patient with history of type 1 Diabetes mellitus Patient with chronic kidney disease
- History of laparotomy and ileus, with chronic intestinal disease
- Patients with acute medical emergencies like diabetic ketoacidosis, renal failure, cardiac failure, any microvascular complications
- Pregnant and lactating womens were excluded.

RESULTS

The present study was carried out by taking 120 subjects divided into two groups A and B. Group A was given with Pioglitazone (15mg) with Metformin (500mg) and Glimipiride (2mg). and Group B was given with Voglibose (0.2mg) with Metformin (500mg) and Glimepiride(2mg).

The number of 120 subjects were included in our study among those the number of subjects in age group 41-50 years were maximum i.e.33 (30.3%).

Gender wise distribution shows that among 120 subjects 72(66%) were males and 48(44%) were females.

The number of 120 patients were included in our study among those in Group A, 33 individuals had DM. Out of these 16 were comorbid with Hypertension and 11 had Tuberculosis. In Group B 36 individuals had DM. Out of these 9 were comorbid with Hypertension and 15 had Tuberculosis.

Table 1: Distribution of patients based on age group.

S. No	Age	Group A	Group B	Total
1	30-40	18	10	28(26.3%)
2	41-50	17	16	33(30.3%)
3	51-60	14	14	28(25.6%)
4	61-70	11	20	31(27.6%)
5	Total	60	60	120(100%)

A total of 120 subjects were included in our study among those the number of subjects in age group 41-50 years were maximum i.e. 33 (30.3%).

Table 2: Gender Wise Distribution.

S. No	Gender	Group A	Group B	Total
1	Male	36	36	72(66%)
2	Female	24	24	48(44%)
3	Total	60	60	120(100%)

In our study among 120 subjects 72(66%) were males and 48(44%) were females

Table 3: Distribution based on comorbidity.

S. No	Drug Group	Diabetes mellitus	DM with Hypertension	DM with Tuberculosis	Total
1	Group A	33	16	11	60
2	Group B	36	9	15	60

In our study among 120 patients in Group A, 33 individuals had DM. Out of these 16 were comorbid with Hypertension and 11 had Tuberculosis. In Group B 36 individuals had DM. Out of these 9 were comorbid with Hypertension and 15 had Tuberculosis.

Distribution of subjects as per 4 weeks blood sugar levels

In our study the mean random blood sugar levels at baseline (4 weeks) were Group A - 194.1 and Group B-221.0mg/dl. the mean fasting blood sugar levels at baseline (4 weeks) were Group A -142.5 and Group B-154.5mg/dl. the mean post prandial blood sugar levels at baseline (4 weeks) were Group A -180.9 and Group B-179.

Distribution of subjects as per 8 weeks blood sugar levels

In our study the mean random blood sugar levels at baseline (8weeks) were Group A -171.1 and Group B-211.6mg/dl. The mean fasting blood sugar levelsat(8weeks) were Group A131.8 and Group B-147.7mg/dl. The mean post prandial blood sugar levels at (8weeks) were Group A -168.0and Group B-169.0mg/dl.

Effect of treatment on fasting blood sugar levels in study groups

In our study the mean fasting blood sugar levels at baseline (0weeks) were Group A -176.5 and Group B-161.7mg/dl and at 4weeks were Group A - 142.5 and Group B-154.5mg/dl and at 8 weeks were Group A -131.8 and Group B-147.7 mg/dl. The change in percentage of fasting blood sugar at 8 weeks was Group A -44.7 and Group B-14.0.

Effect of treatment on Random blood sugar levels in study groups

In our study the mean Random blood sugar levels at baseline (0weeks) were Group A -218.6 and Group B-227.8mg/dl and at 4weeks were Group A - 194.1 and Group B-221.0mg/dl and at 8weeks were Group A -171.8 and Group B-181.0 mg/dl. The change in percentage of fasting blood sugar at 8 weeks was Group A -47.5 and Group B-39.8.

Effect of treatment on post prandial blood sugar levels in study groups

In our study the mean Post prandial blood sugar levels at baseline (0weeks) were Group A -205.2 and Group B-183.0mg/dl and at 4weeks were Group A -180.9 and Group B-176.0mg/dl and at 8weeks were Group A -168.0 and Group B-150.0 mg/dl. The change in percentage of fasting blood sugar at 8 weeks was Group A -37.2 and Group B-33.0

Effect of treatment on HbA1c levels in study group

In our study the mean HbA1c at baseline (0weeks) were Group A -8.4 and Group B-8.7mg/dl and at 12 weeks were Group A -6.6 and Group B- 7.6mg/dl. The change in percentage of HbA1c at 12 weeks was Group A - 1.8 and Group B-1.1.

Table 4: Safety parameters.

S. No	Parameters	Group A	Group B
1	Edema	2	0
2	Headache	2	1
3	Flatulence	0	2
4	Abdominal discomfort	0	5

The adverse effects in group B subjects were maximum when compared to group B.

DISCUSSION

Effect of treatment on FBS, PPBS and HBA1c levels in subjects.

In our study the mean fasting blood sugar levels at baseline (0weeks) were Group A -176.5 and Group B-161.7mg/dl and at 4weeks were Group A -142.5 and Group B-154.5mg/dl and at 8 weeks were Group A -131.8 and Group B-147.7 mg/dl. The change in percentage of fasting blood sugar at 8 weeks was Group A -44.7 and Group B-14.0.

The difference between two treatment values (0 weeks and 12 weeks) of Group A and Group B shows statistical significance. (P=6.8) Table 6.8.

In our study the mean Random blood sugar levels at baseline (0weeks) were Group A -218.6 and Group B-227.8mg/dl and at 4weeks were Group A -194.1 and Group B-221.0mg/dl and at 8weeks were Group A -171.8 and Group B-181.0 mg/dl. The change in percentage of fasting blood sugar at 8 weeks was Group A -47.5 and Group B-39.8.

The difference between two treatment values (0 weeks and 12 weeks) of Group A and Group B shows statistical significance. (P= 0.109) Table 6.9.

In our study the mean Post prandial blood sugar levels at baseline (0weeks) were Group A - 205.2 and Group B-183.0mg/dl and at 4weeks were Group A -180.9 and Group B-176.0mg/dl and at 8 weeks were Group A -168.0 and Group B- 150.0 mg/dl. The change in percentage of fasting blood sugar at 8 weeks was Group A -37.2 and Group B-33.0.

The difference between two treatment values (0 weeks and 12 weeks) of Group A and Group B shows statistical significance.(P= 0.37) Table 6.10.

In our study the mean HbA1c at baseline (0weeks) were Group A -8.4 and Group B-8.7mg/dl and at 12 weeks were Group A -6.6 and Group B- 7.6mg/dl. The change in percentage of HbA1c at 12 weeks was Group A -1.8 and Group B-1.1.

CONCLUSION

The present study demonstrated that both pioglitazone and voglibose, when used as adjuncts to glimepiride and metformin, effectively improved glycemic control in patients with Type 2 Diabetes Mellitus. However, pioglitazone showed a greater reduction in HbA1c and fasting blood glucose levels compared to voglibose, indicating superior efficacy in overall glycemic management.

Both voglibose and pioglitazone can be effective adjuncts to glimepiride and metformin. Treatment decisions should be individualized based on patient profiles, including glycemic patterns, and tolerance to side effects. Though pioglitazone and voglibose were equally effective, yet pioglitazone showed better results in controlling glycaemic profile (FBG, PPBG) and in lowering HbA1c as compared to voglibose. moreover, pioglitazone had minimal side effects as compared to

voglibose.

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