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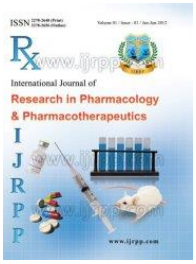

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Research article ***Open Access***

An prospective and observational study of comparison of efficacy and tolerability between metformin and combination of metformin and glibenclamide in the maintence therapy of type 2 diabetes mellitus in a tertiary care hospital

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ABSTRACT

Background

Diabetes mellitus is one of the most common non-communicable disease world-wide. There are many groups of drugs available for the treatment of type 2 diabetes mellitus. we use these drugs as monotherapy or in combination to maintain normoglycemia. Because of paucity of published reports in the Indian literature regarding the pattern of use, efficacy, safety, tolerability of comparison of therapy of metformin and combination of metformin and glibenclamide, the present study was taken up.

Objectives

To study the comparison of efficacy, safety and tolerability of metformin and combination of metformin and glibenclamide in achieving normal blood glucose level in type 2 diabetes mellitus.

Materials and methods

100 properly selected subjects with type 2 diabetes mellitus were included for the present study. The medication were used empirically as monotherapy or fixed dose combination, OD or BID in a continuation manner after the meals. Blood glucose level was measured at the baseline and daily afterwards for one month using standard techniques. The data collected was analyzed statistically using descriptive statistics. Tolerability and patient compliance for the prescribed medications were also assessed during the follow up visits.

Results

Combination therapy reported to control the blood glucose level more efficiently as compared to metformin monotherapy at the end of the study, as 96% of subjects showed normoglycemia as compared to metformin (70%). Also, incidence of hyperglycemic episodes were less in combination therapy. Subjects with combination therapy reported more side effects compared to metformin alone therapy. The patient compliance for the prescribed medications was excellent.

Interpretation and Conclusion

Blood glucose level can be effectively maintained under normal limits in Type 2 DM, with combination therapy as compared to monotherapy of metformin.

Keywords: Diabetes mellitus, Metformin, Glibenclamide.

INTRODUCTION

Diabetes mellitus is one of the most common non-communicable disease world-wide. Earlier named as disease of the rich, now it is seen in nearly all socio-economic classes, both in male and in females, and in nearly all age groups. There are many groups of drugs available for the treatment of type 2 diabetes mellitus. we use these drugs as monotherapy or in combination to maintain normoglycemia. Because of paucity of published reports in the Indian literature regarding the pattern of use, efficacy, safety, tolerability of comparison of therapy of metformin and combination of metformin and glibenclamide, the present study was taken up.

REVIEW OF LITERATURE

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Many factors are contributing to hyperglycemia for example: reduced insulin secretion, decreased glucose utilization, and increased glucose production. There are a lot of etiological factors that causes or predispose an individual to DM such as genetic factors, immune-mediated factors, idiapathic, diseases of the exocrine pancreas, endocrinopathies, drugs, infections etc. DM is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases. [1]

Classification

DM is classified into two broad categories, type 1 and type 2. Type 1 diabetes is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. [1]

Epidemiology

The worldwide prevalence of DM has risen dramatically over the past two decades. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. [1]

Pathogenesis

Type 1 DM

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to the destruction of the pancreatic beta cells and insulin deficiency. Type 1 DM results from autoimmune beta cell destruction and most, but not all, individuals have evidence of islet-directed autoimmunity. [1]

Type 2 DM

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Type 2 DM has a strong genetic component. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40%. The disease is polygenic and multifactorial, as environmental factors (such as obesity, nutrition, and physical activity) also has their effects on the occurrence of DM. Type 2 DM is also characterized by excessive hepatic glucose production, and abnormal fat metabolism. In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output but as the insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. [1]

Clinical Findings

The principal clinical features of the two major types of diabetes mellitus are:[2]

Clinical features of diabetes at diagonosis	Type 1 DM	Type 2 DM
Polyuria and thirst	++	+
Weakness or fatigue	++	+
Polyphagia with weight loss	++	-
Recurrent blurred vision	+	++
Vulvovaginitis or pruritis	+	++

Peripheral neuropathy	+	++
Nocturnal enuresis	++	-
Often asysptomatic	-	+

Complications of DM

Diagnosis of diabetes is often delayed leading to prolonged periods of uncontrolled hyperglycemia and consequent risk of acute and chronic complications, so early detection of DM is essential for better management. [24, 25]

Acute Complications of DM

Diabetic ketoacidosis (DKA), particularly seen in type 1 DM and Hyperglycemic Hyperosmolar State (HHS), primarily seen in type 2 DM, are acute complications of diabetes. [1]

Chronic Complications of DM

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. The vascular complications of DM are divided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease). Nonvascular complications include problems such as gastroparesis, infections, cataract, glicoma, hearing loss and skin changes. [1]

Diagnosis

The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM based on the following premises: [1, 8]

1. The spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load (OGTT—oral glucose tolerance test) varies among normal individuals, and
2. DM is defined as the level of glycemia at which diabetes-specific complications occur as compared to normal population.

Criteria for the Diagnosis of Diabetes Mellitus : 4 options

	Normal glucose level	**Chance of impaired glucose tolerance (prediabetes)**	**Chance of diabetes**
1.Symptoms of diabetes plus random blood glucose	Less than 140 mg/dL	140 to 199 mg/dL	More than 200 mg/dL
2.Fasting plasma glucose	Less than 100 mg/dL	110 to 125 mg/Dl	More than 126 mg/dL
3. Two-hour plasma glucose during an oral glucose tolerance test	Less than 140 mg/dL	140 to 199 mg/dL	More than 200 mg/dL
4. Hb A1C	Below 6% (42mmol/mol)	6.0% to 6.4% (42 to 47 mmol/mol)	6.5% or over (48 mmol/mol or over)

a. Random is defined as without regard to time since the last meal.
b. Fasting is defined as no caloric intake for at least 8 hour.
c. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.
d. *Performed in a lab using NGSP-certified method and standardized to DCCT assay*

MANAGEMENT OF DIABETES MELLITUS

Approach to the Patient

The history and physical examination should assess for symptoms or signs of acute hyperglycemia and should screen for the chronic complications and conditions associated with DM. [1]

History

A complete medical history should be obtained with special emphasis on DM-relevant aspects such as weight, family history of DM and its complications, risk factors for cardiovascular disease, exercise, smoking, and ethanol use. Symptoms of

hyperglycemia include polyuria, polydipsia, weight loss, fatigue, weakness, blurry vision, frequent superficial infections, and slow healing of skin lesions after minor trauma. [1]

Physical Examination

A complete physical examination should be done such as weight or BMI, retinal examination, orthostatic blood pressure (consider hypertensive if blood pressure is > 130/80 mmHg) , foot examination, peripheral pulses, ankle reflexes, any superficial fungal infections or evidence of peripheral neuropathy etc. [1]

LIFESTYLE INTERVENTIONS

Nutrition

Medical nutrition therapy (MNT) is a term used by the American Diabetes Association (ADA) to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, weight loss). The ADA has issued recommendations for three types of MNT. 1. Primary prevention measures of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with pre-diabetes) by promoting weight reduction.

Secondary prevention measures of MNT are directed at preventing or delaying diabetes-related complications in diabetic individuals by improving glycemic control.

Tertiary prevention measures of MNT are directed at managing diabetes-related complications (cardiovascular disease, nephropathy) in diabetic individuals.

As for the general population, a diet that includes fruits, vegetables, fiber-containing foods, and low-fat milk is advised. [1]

Exercise

Exercise has multiple positive benefits like cardiovascular risk reduction, reduced blood pressure, maintenance of muscle mass, reduction in body fat, and weight loss. It reduces plasma glucose and increasing insulin sensitivity. In patients with diabetes, the ADA recommends 150 min/week (distributed over at least 3 days) of aerobic physical activity. In patients with type 2 DM, the exercise regimen should also include resistance training. [1]

Pharmacologic Therapy

Without adequate blood-glucose-lowering treatment, blood glucose levels may rise progressively over time in people with type 2 diabetes. [34] Various groups of drugs used in different types of DM can be classified according to their mechanisms of action as. [3]

1. Insulin : different types of insulin preparations and insulin analogues
2. Drugs which enhance insulin secretion : Sulfonylureas, Meglitinide analogues, New groups like Glucagon-like peptide-1 receptor agonists and Dipeptidyl peptidase-4 inhibitors [12].
3. Drugs which overcome insulin resistance : Biguanides, Thiazolidinediones
4. Other drugs used in DM : a-Glucosidase inhibitors, Amylin analogue, Dopamine-D2 receptor agonist, Sodium-glucose cotransport-2 inhibitors

Monotherapy therapy for DM

Monotherapy is given as first-line treatment for newly diagnosed patients of DM with exercise and diet management. Metformin is prefer as monotherpy as it is better tolerated, glibenclamide is not considered because sulfonylureas are associated with major adverse cardiovascular events (MACE), macrosomia and neonatal hypoglycemia in gestational diabetes. [14, 15, 16, 18, 20, 28, 31, 36, 42, 43, 52]

Combination therapy for DM

Different oral hypoglycemic drugs are prescribed in combination for effective control of blood glucose level. Combination of glibenclamide (glyburide in the U.S.) and metformin simultaneously addresses two different but complimentary mechanisms to improve glycemic control in type 2 diabetes. The negative influence of the concealed dysfunctional NO effects induced by glibenclamide or high glucose on beta-cell activity can be counteracted by metformin resulting in synergism of anti-diabetic action.[48] Metformin and acarbose or canagliflozin or linagliptin combination has better HbA1c reduction. [17, 30, 41, 47] Rosiglitazone and glyburide is seen to be effective for patients with type 2 diabetes previously inadequately controlled with sulfonylurea monotherapy.[19] Combination therapies resulted in

largest reductions in HbA1c than metformin or glyburide monotherapy. [27, 29, 37]

MATERIALS AND METHODS

100 properly selected subjects with type 2 diabetes mellitus were included for the present study. The medication were used empirically as monotherapy or fixed dose combination, OD or BID in a continuation manner after the meals. Blood glucose level was measured at the baseline and daily afterwards for one month using standard techniques. The data collected was analyzed statistically using descriptive statistics. Tolerability and patient compliance for the prescribed medications were also assessed during the follow up visits.

RESULTS

Table 1: Age distribution (n=100)

Age group	Total number of patients	Number of patients with metformin treatment	Number of patients with combination therapy
0-18	0	0	0
19-60	60	28	32
>60	40	22	18
Total	100	50	50

Table 2: Gender distribution (n=100)

Gender	Total number of patients	Number of patients with metformin treatment	Number of patients with combination therapy
Female	45	20	25
Male	55	30	25
Total	100	50	50

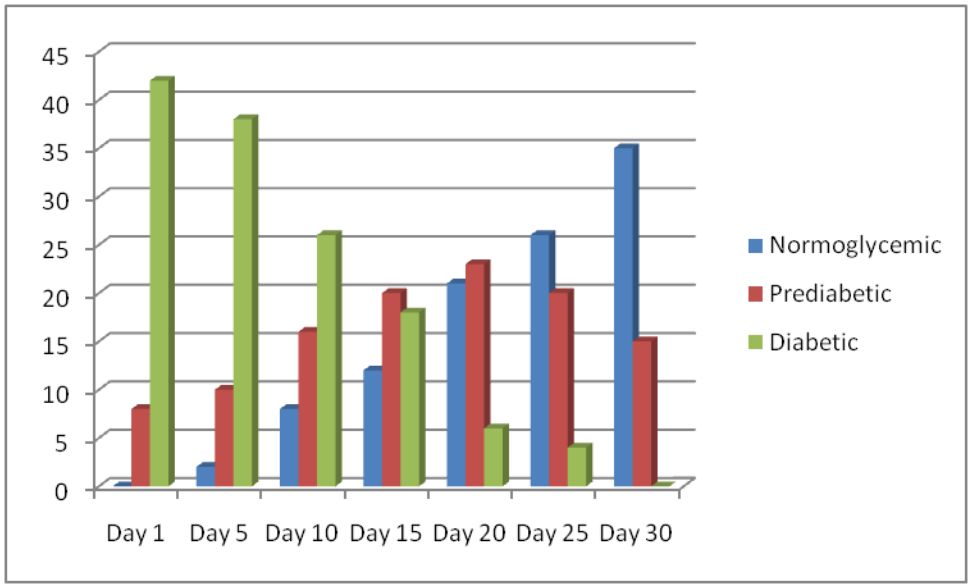
Table 3: Number of patients, with blood glucose levels, on day 1, baseline (n=100)

Random blood glucose	Total number of patients	Number of patients with metformin treatment	Number of patients with combination therapy
Normoglycemic	0	0	0
Prediabetics	15	8	7
Diabetics	85	42	43
Total	100	50	50

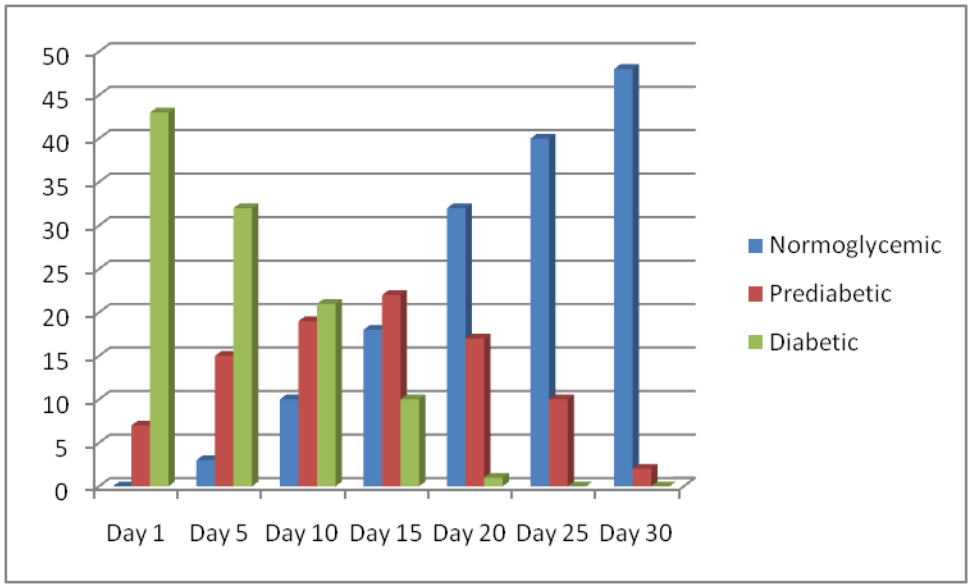
Graded as per ADA, Criteria for the Diagnosis of Diabetes Mellitus: Symptoms of diabetes plus random blood glucose (all the subjects had symptoms of diabetes mellitus)

Table 4: Blood glucose level of the patients on different days of the study

	Metformin treatment			Combination therapy			
Visits	Normoglycemic	Prediabetic	Diabetic	Normoglycemic	Prediabetic	Diabetic	Total
Day 1	0	8	42	0	7	43	100
Day 5	2	10	38	3	15	32	100
Day 10	8	16	26	10	19	21	100
Day 15	12	20	18	18	22	10	100
Day 20	21	23	6	32	17	1	100
Day 25	26	20	4	40	10	0	100
Day 30	35	15	0	48	2	0	100



Graph 1: Comparison of blood glucose level of patients on Metformin treatment at selected intervals
Note: number of patients on y axis and days on x axis



Graph 2: Comparison of blood glucose level of patients on combination therapy at selected intervals
Note: number of patients on y axis and days on x axis.

DISCUSSION

The present study is an observative study of comparison of efficacy and tolerability between Metformin and combination of Metformin and Glibenclamide in the maintaince of Type 2 Diabetes Mellitus in a Tertiary care hospital. Patients are given either metformin 500mg tablet twice a day or combination of metformin 500mg and glibenclamide 5mg (instead of 2.5mg) [9] tablet single dose after meals on daily basis to different study groups.

The age distribution of the study subjects is shown in the table 1. Majority of the patients (60%) were between 19 to 60 years age group. And rest (40%) were above 60 years age group. They were nearly equally distributed between the study groups at appropriate age groups.

The gender distribution of the study subjects is shown in the above table 2. Male patients are slightly more (55%) as compared to female patients, but equally distributed in both the study groups.

The main features looked in the study is recording of random blood glucose level and taking full history of clinical features of the patients (as one of the option in criteria for DM diagnosis in American Diabetic Association, ADA)[8] on the daily basis for the period of one month. Patients are asked about the daily symptoms and signs are seen on daily check-ups. Random blood glucose is investigated in the laboratory of all the subjects and recorded on daily basis. The objective parameters i.e recording of Random blood glucose level at base line (day-1) have been summarized in the following table:

Table 3 shows the number of patients of the study groups at the presenting day (day 1). Random blood glucose is graded as per ADA, as normoglycemic (less than 140 mg/dL), prediabetics (140 to 199 mg/dL) or diabetics (more than 200 mg/dL). On the day 1, all subjects were presented with clinical features of DM. No patients showed normal blood glucose on day 1. Most of the patients (n=85) had diabetic level of blood glucose, some with prediabetic level of blood glucose (n=15).. Patients with different grades were nearly equally distributed in both the study groups. There is not much difference in the distribution of patients with different grading.

Table 4 shows the recording of Random blood glucose of all the patients at different days of the study, with metformin and combination therapy. For convenience, Random blood glucose recording at selected intervals are taken into consideration. Almost all the patients are having chronic DM and are on different drug therapy. Day 1 recording is the baseline of the study. On day 5, out of 100 patients, 70 patients recorded diabetic level of random blood glucose, 38 in metformin and 32 in combination therapy. On day 15, random blood glucose level of 42 pateints was prediabetics (20 with metformin, 22 with combination therapy) shows normal blood pressure. On day 20, 53 patients (21 with metformin, 32 with combination therapy) showed normal random blood glucose. And on day 25, all the four patients with diabetic level of random blood glucose were in metformin therapy. Random blood glucose level of all the patients return to normal level in combination therapy and 35 patients in metformin therapy at the end of the day 30.

The above bar graph 1 shows the comparison of random blood glucose level of all patients on metformin treatment at selected intervals. As the days progressed, many patients with decrease in blood glucose level. At the end of one month, 35 patients showed normoglycemia with still 15 patients showing prediabetic level of random blood glucose.

The above bar graph 2 shows the comparison of random blood glucose level of all patients on combination therapy at selected intervals. As the days progressed, random blood glucose level decreases. At the end of one month, almost all subjects had normal random blood glucose level.

Merformin

Metformin is the only member of the biguanide class of oral hypoglycemic drugs available for use today. Metformin increases the activity of the AMP-dependent protein kinase (AMPK). The net result of these actions is increased glycogen storage in skeletal muscle, lower rates of hepatic glucose production, increased insulin sensitivity, and lower blood glucose levels. Several models were used for exploring signaling pathways for understanding the drug action, as metformin shows phramacogenetics variations. Metformin's negligible risk of hypoglycemia in monotherapy and few drug interactions of clinical relevance give this drug a high safety profile. [4,3,5,6.7.33,35,49,50,53]

Metformin is currently the most commonly used oral agent to treat type 2 diabetes and is generally accepted as the first-line treatment for this condition. Treatment of high-risk subjects with metformin results in reduction in the risk of diabetes. Metformin is not effective in the treatment of type 1 diabetes. Metformin is also been trying in cancer therapy and for polycystic ovarian disease. The most common side effects of metformin are gastrointestinal. However , incidence of lactic acidosis very rare compared to the banned phenformin dug. Weight loss is seen with some individuals due to anorexia. Metformin is contraindicated in chronic kidney disease, so serum creatinine should be measured before prescribing. [20,21,22,23,39,40,51,54,55]

Glibenclamide

Glibenclamide belongs to second generation Sulnonylureas (K_{ATP} Channel Modulators) groups of oral hypoglycaemic drugs. They provoke brisk release of insulin from pancreas. Hypoglycaemia is the most commonest and sometime fatal adverse effects of glibenclamide. weight gain is a common side effect seen with many persons. Glyburide can

acutely reduce key neuroendocrine and metabolic counterregulatory defenses during hypoglycemia in healthy individuals. [3,4,5,6,32]

All the patients of both the study groups good compliance, as assessed by daily asking about medications intake and daily random blood glucose check-ups. Some fluctuations (increase or decrease in blood glucose levels) are seen in both the study groups, more with metformin group. Hypoglycemic attacks are more commonly seen with combination therapy. Comparatively, When added to metformin, gliclazide was associated with the lowest risk of hypoglycaemia between the newer generation Sulfonylureas. [45, 46]

Adverse effects such as vomiting, abdominal pain, nausea etc are seen in both the study groups, more commonly with the combination therapy. Weight loss is seen in some individuals in metformin therapy, with a history of taking the medicine for long duration.

Combination of metformin and glibenclamide appears to control the blood glucose level more efficiently as compared to metformin monotherapy, as at the end of the study, 96% of subjects showed normoglycemia as compared to metformin (70%). The same is compared with other previous studies [10, 11, 26]. Also, incidence of hyperglycemic episodes were less in combination therapy. Addition of Vildagliptin or rosiglitazone is better option for patients failing on metformin plus glyburide particularly in patients with baseline HbA1c ≤8%. [38, 44]

CONCLUSION

Blood glucose level can be effectively maintained under normal limits in Type 2 DM, with combination therapy as compared to monotherapy with metformin. However, only metformin can be use as initial therapy in newly diagnosed DM patients. Subjects with combination therapy reported more side effects compared to metformin alone therapy. The patient compliance for the prescribed medications was excellent.

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