TYPE 2 DIABETES MELLITUS;
COMPARISON OF EFFICACY OF REPAGLINIDE AND METFORMIN IN THE TREATMENT OF NEW ONSET TYPE 2 DIABETES MELLITUS.

Dilshad Muhammad¹, Masood Javed², Muzzammal Iftikhar³

ABSTRACT… Background: Diabetic complications are related to impaired glycemic control. Repaglinide, short-acting insulin secretagogues, has excellent anti-hyperglycemic effect and a lower risk of hypoglycemia. However, whether repaglinide can be used as an initial therapy in patients with newly diagnosed T2DM is still unconfirmed. Objectives: The objective of this study was: To compare efficacy of Repaglinide and Metformin in the Treatment of New Onset Type 2 Diabetes Mellitus. Study Design: Randomized Controlled Trial. Setting: District headquarter Hospital, Faisalabad. Period: 6 Months (Jan 2018 to June 2018). Methodology: Patients were randomly divided into two groups (A & B) by using computer generated random number table. Group A was given repaglinide 0.75-1.5 mg/day while group B received metformin 750-1500mg/day. The doses of metformin and repaglinide were adjusted according to blood glucose level. Group A was given repaglinide 0.75-1.5 mg/day while group B received metformin 750-1500mg/day. The doses of metformin and repaglinide were adjusted according to blood glucose level. For HbA1C and FBS, blood samples were sent to pathology laboratory at the start of study and after 3 months. Follow up was ensured by reaching the patients through telephonic contact. Data was collected through self-conducted interviews using a standardized Performa. Results: In our study, mean±sd was calculated as 44.54±5.92 years in Group-A and 45.31±6.13 years in Group-B, 42.86%(n=15) in Group-A and 40%(n=14) in Group-B were male whereas 57.14%(n=20) in Group-A and 60%(n=21) in Group-B were females. Baseline mean HbA1c levels of the patients were calculated as 7.51±0.50 mmol/L in Group-A and 7.54±0.52 mmol/L in Group B, p value was 0.81. After treatment, these findings were reduced to 5.57±0.65 in Group-A and 6.4±0.49 in Group-B, p value was 0.0001. At baseline mean fasting blood glucose levels of the patients were calculated as 7.43±0.56 mmol/L in Group-A and 7.46±0.50 mmol/L in Group B, p value was 0.82. After treatment, these findings were reduced to 5.83±0.71 in Group-A and 6.29±0.67 in Group-B, p value was 0.007. Conclusion: We concluded that on comparison of Metformin and Repaglinide monotherapy in the Treatment of New Onset Type 2 Diabetes Mellitus in terms of mean fasting blood glucose and mean HbA1c, both drugs reduced HbA1c and fasting blood sugar but Repaglinide was found significantly better for reduction of HbA1c and fasting blood sugar when compared to Metformin.

Key words: Fasting Blood Sugar, HbA1c, Metformin, New Onset of Type 2 Diabetes Mellitus, Repaglinide.

INTRODUCTION
Type 2 diabetes mellitus (T2DM) is a condition which has heavy financial and social burden in it is management.¹ Although Diabetes mellitus is a worldwide problem it is prevalence has recently increased throughout Asia as well.² Insulin resistance is considered to play an integral role in pathogenesis in development of T2DM. In addition physical inactivity, inheritance and eating habits etc. also contributes in the development of T2DM.³ A Study showed that control of T2DM is not up to the mark in the developed countries in about 2/3⁴ of patients and this fact is even more pronounced in the developing countries.⁴

In Pakistan, the prevalence T2DM is quite high and approximately 6.3 million people have this disease. This is likely to increase and by 2030 about 11.4 million peoples will have diabetes if appropriate measures are not taken.⁵ Glucose impairment is one of the risk factor for CVD, which
is one of the Major cause of death.\textsuperscript{6}

T2DM needs an optimal control and for this a multidisciplinary action is required. It is proved in various clinical studies that intensive treatment reduces micro and macro vascular complications.\textsuperscript{7}

Metformin is commonly used anti diabetic drug for the management of T2DM. It decreases gluconeogenesis in liver, increases uptake of glucose, decreases glucose absorption from GIT and increase the sensitivity of insulin.\textsuperscript{8,9}

Repaglinide is short-acting insulin secretagogues with biliary excretion that, increases insulin secretion immediately after meals and also corrects abnormal insulin secretion.\textsuperscript{10}

In one study by J. Ma et al it was found that both metformin and repaglinide decreases fasting blood glucose level without any major difference that is (6.29±0.11 mmol/L \( P <0.01 \)) and (6.46±0.14mmol/L \( P<0.01 \)) respectively. On the other hand repaglinide group has more effect on HbA1c as compared to metformin group (metformin 6.34±0.08%, \( P < 0.01 \) and repaglinide 6.28±0.09%, \( P <0.01 \)).\textsuperscript{11}

There are only few studies available in T2DM Pakistani patients which compares the efficacy of these two drugs. This study will compare the effect of metformin and repaglinide monotherapy on both FBS and HBA1c in T2DM Pakistani patients.

**OBJECTIVE**
The objective of this study was:
To compare efficacy of Repaglinide and Metformin in the Treatment of New Onset Type 2 Diabetes Mellitus.

**OPERATIONAL DEFINITIONS**

**Type II Diabetes Mellitus**
Type II Diabetes Mellitus FBS of 126mg/dl or more and PPBS level of 200mg/dl or more measured by a standard laboratory on two occasions establishes the diagnosis of diabetes mellitus.

**Fasting Blood Glucose**
A measurement of the concentration of glucose in the plasma after the patient has not eaten for at least 8 hour which was measured at twelve weeks.

**HBA1c**
HbA1c means glycated haemoglobin (A1c), which shows average plasma glucose levels which was measured at twelve weeks of treatment.

**MATERIAL AND METHODS**

**Study Design**
Randomized Controlled Trial.

**Setting**
District headquarter Hospital, Faisalabad.

**Duration of Study**
6 Months (Jan 2018 to June 2018).

**Sample Size**
Sample size was calculated according to WHO sample size calculator.
Sample size = 70 (35 per group)

**Sampling Technique**
Non-Probability Consecutive Sampling

**SAMPLE SELECTION**

**Inclusion Criteria**
- Newly diagnosed diabetes mellitus type 2 patients within one year
- Both genders
- Patients aged between 30 and 60 years
- Patients with BMI between 18.5 to 24.9

**Exclusion Criteria**
- Patients with existing coronary artery disease
- Patients with disturb abnormal renal function
- Patient with liver disease or severe gastrointestinal disease
- Pregnant and lactating women

**DATA COLLECTION PROCEDURE**
Those patients who met inclusion criteria were enrolled in the study. From each participant of
the study informed consent was taken. Patients were divided into group A & B by using computer generated random number table. Group A received repaglinide 0.75-1.5 mg/day group B received metformin 750-1500mg/day. The levels of blood glucose were taken and doses of repaglinide and metformin were adjusted accordingly. Blood samples of FBS and HbA1c were sent at start and after three months to pathologist for reporting. Telephonic contact with patients was established and follow up was ensured. Data was collected using a standardized Performa by principal investigator by personal contact.

**DATA ANALYSIS PROCEDURE**

Analysis of the available data was done through SPSS version 20. Mean and standard deviation was calculated for all quantitative variables like age, BMI, duration of disease, HbA1C and FBS at baseline and at 12 weeks. Frequency and percentage was calculated for all qualitative variables like gender. Independent sample t test was applied to compare mean in HbA1C and FBS in both groups. P value of < 0.05 was taken as important. Effect modifiers like age, duration of disease, gender and BMI were controlled by stratification. Post stratification independent sample t-test was applied.

**RESULTS**

According to the criteria, 70 cases (35 per group) were included in the study to compare Repaglinide and Metformin monotherapy in the Treatment of New Onset Type 2 Diabetes Mellitus.

Age distribution shows that 51.43% (n=18) in Group-A and 40% (n=14) in Group-B were between 30-45 years of age while 48.57% (n=17) in Group-A and 60% (n=21) in Group-B were between 45-60 years of age, mean+sd was calculated as 44.54±5.92 in Group-A and 45.31±6.13 years in Group-B. (Table-I)

Gender distribution shows that 42.86% (n=15) in Group-A and 40% (n=14) in Group-B were male whereas 57.14% (n=20) in Group-A and 60% (n=21) in Group-B were females. (Table-II)

Mean BMI of the patients was recorded as 34.14±2.06 in Group-A and 34.71±2.25 in Group-B. (Table-III)

At baseline mean HbA1c levels of the patients were calculated as 7.51±0.50 mmol/L in Group-A and 7.54±0.52 mmol/L, p value was 0.81, after treatment, these findings were reduced to 5.57±0.65 in Group-A and 6.4±0.49 in Group-B, p value was 0.0001, on comparison within the group, both groups showed significant decrease in HbA1c levels but Group-A showed a significant more decrease in HbA1c. (Table-IV)

At baseline mean fasting blood glucose levels of the patients were calculated as 7.43±0.56 mmol/L in Group-A and 7.46±0.50 mmol/L, p value was 0.82. After treatment, these findings were reduced to 5.83±0.71 in Group-A and 6.29±0.67 in Group-B, p value was 0.007. On comparison within the group, both groups showed significant decrease in FBS levels but Group-A showed a significant more decrease in fasting blood glucose. (Table-V).

<table>
<thead>
<tr>
<th>Age (in Years)</th>
<th>Group-A (n=35)</th>
<th>Group-B (n=35)</th>
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<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
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<tr>
<td>30-45</td>
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<td>45-60</td>
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<td>Mean+SD</td>
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Table-I. Age distribution (n=70)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group-A (n=35)</th>
<th>Group-B (n=35)</th>
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<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
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<tr>
<td>Male</td>
<td>15</td>
<td>42.86</td>
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<tr>
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<td>20</td>
<td>57.14</td>
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Table-II. Gender distribution (n=70)

<table>
<thead>
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<th>Group-B (n=35)</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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Table-III. Mean BMI of the patients (n=70)
DISCUSSION

Diabetic complications are related to impaired glycemic control. Treatment with Metformin in obese T2 diabetic patients reduces HBA1c and its complications. So metformin is the first drug used after the life style modification in this patients.

Repaglinide, short-acting insulin secretagogues, has excellent anti-hyperglycemic effect and a lower risk of hypoglycemia. However, it is not documented that it can be used for initiation of therapy in newly diagnosed T2DM patients.

We compared our results with a previous study by J. Ma et al11 in which it was found that both metformin and repaglinide decreases fasting blood glucose level without any major difference that is (6.29±0.11 mmol/L P <0.01) and (6.46±0.14mmol/L P<0.01) respectively. On the other hand repaglinide group has more effect on HbA1c as compared to metformin group that is (metformin 6.34±0.08%, P < 0.01 and repaglinide 6.28±0.09%, P <0.01).11 These findings are comparable with this study but we do not agree regarding fasting blood glucose. In our study, we saw that both the drugs were effective in FBS and HbA1c reduction in newly diagnosed type 2 patients. After a trial of 3 months there was statistically significant difference in decrease of FBS between repaglinide and metformin. The reduction in HbA1c with repaglinide was significantly greater than that of metformin. As the post prandial glucose levels were not in our study but from greater reduction in HbA1c levels with repaglinide, we can infer that there is marked reduction in post prandial glucose with repaglinide.

To control glycemic variability in patients with newly diagnosed T2DM repaglinide and metformin can be used. It is proved that both Acute and sustained hyperglycemia results in diabetic complications. It is seen that acute changes in blood glucose level were more dangerous as compared to chronically high blood glucose level to endothelial cells and human kidney proximal tubule cells. Various clinical studies have used changes in glucose level as therapeutic target and in this respect various drugs have shown to decrease the variability in blood glucose level12-14

F-S Fang and others15 compared the effect of repaglinide and metformin initial monotherapy in newly diagnosed type 2 diabetes mellitus Chinese patients and found that both this treatment modalities had comparable effect in improving the glucose level and reducing the glycemic variability, increasing sensitivity of insulin and improving the Beta cell functions. Therefore, repaglinide can be used as initial therapy in newly diagnosed T2DM Chinese patients.

Søren S Lund et al16 studied the effect of metformin and repaglinide, in newly diagnosed T2DM non-obese patients, on cardiovascular risk markers related to inflammation and endothelial dysfunction and found Metformin was more effective in reducing selected biomarkers reflecting inflammation and endothelial dysfunction compared with repaglinide despite similar blood glucose levels in both modalities. In this respect more studies are needed to clarify the situation.

CONCLUSION

We concluded that on comparison of Metformin and Repaglinide monotherapy in the Treatment of New Onset Type 2 Diabetes Mellitus in terms of mean fasting blood glucose and mean HbA1c,
both drugs reduced HbA1c and fasting blood sugar but Repaglinide was found significantly better for reduction of HbA1c and fasting blood sugar when compared to Metformin.

**REFERENCES**


**Worry** often gives a small thing a great **shadow**.

"Swedish Proverb"

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### AUTHORSHIP AND CONTRIBUTION DECLARATION

<table>
<thead>
<tr>
<th>Sr. #</th>
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<tr>
<td>1</td>
<td>Dilshad Muhammad</td>
<td>Research work and paper writing.</td>
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<tr>
<td>2</td>
<td>Masood Javed</td>
<td>Contributed conception supervision and proof reading.</td>
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<tr>
<td>3</td>
<td>Muzzammal Iftikhar</td>
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