RESEARCH ARTICLE

A comparative study to evaluate the efficacy of metformin monotherapy on glycemic markers in normal weight, over weight, and obese patients with Type 2 diabetes mellitus

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ABSTRACT

Background: Metformin has been recommended as pharmacological therapy of first choice in Type 2 diabetes mellitus (T2DM) but there remains a gap in the present literature regarding relative efficacy and choice of metformin as monotherapy in patients who are non-obese when compared to obese. Aim and Objectives: The aim of the study was to evaluate the efficacy of Metformin as monotherapy on glycemic markers in normal weight, over weight, and obese T2DM patients. Materials and Methods: After obtaining permission from institutional ethics committee, 90 treatment naïve patients with T2DM who met inclusion criteria were included in this study. They were categorized into normal weight, over weight, and obese based on BMI. Efficacy was measured by reduction in glycemic parameters at end of weeks 4, 8, 12, and 16 from baseline. Safety was assessed by monitoring adverse events. Data analyzed using analysis of variance, Student t-test for continuous data and Chi-square test for categorical data. Results: There was a significant decrease in glycosylated hemoglobin, fasting blood sugar, and postprandial blood sugar levels from baseline to end of 16 weeks in all three groups (P < 0.001) but the difference was not statistically significant between the three groups (P > 0.05). A significant decrease in body weight was observed in overweight and obese group whereas the reduction (0.3 Kg) is not significant in normal weight group. The treatment was well tolerated in all three groups. Conclusion: Metformin in normal weight group was found to be as efficacious as that of overweight and obese group for treating newly detected T2DM. Furthermore, the weight loss in normal weight group is negligible compared to overweight and obese group patients.

KEY WORDS: Metformin; Diabetes mellitus; Normal weight; Obese; Glycemic parameters

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by variable degrees of insulin resistance as well as progressive deterioration in the function of pancreatic β cells resulting in impaired insulin secretion which leads to hyperglycemia and subsequent complications such as coronary artery disease, peripheral vascular disease, retinopathy, nephropathy, and neuropathy.[1] According to the International Diabetic Federation (IDF) report 2019, 463 million people were suffering with DM globally and 77 million in India.[2] India is being the diabetic capital of the world with a projected 134.3 million individuals with diabetes by 2045.[3]

Metformin has been recommended as pharmacological therapy of first choice in T2DM by the American Diabetes Association (ADA) and European Association for the
Study of Diabetes. Its potent blood glucose lowering efficacy, beneficial effects on body weight and lipid profile, proven safety record, low cost, and protective effect on the cardiovascular system have secured its place as the favored initial drug in contrast to other oral anti-diabetic drugs.

However, there remains a gap in the present literature regarding relative efficacy of metformin as monotherapy in patients who are non-obese when compared to obese. Although in western countries large proportion of individuals with Type 2 diabetes are obese, the situation is reverse in Asia pacific region and India where in 64% of them are normal weight. Due to the paucity of existing data, this study has been planned to evaluate the efficacy of metformin as monotherapy on glycemic markers in normal weight, overweight, and obese individuals with newly diagnosed T2DM.

MATERIALS AND METHODS

This study was conducted on out-patient basis at the medicine department of Victoria Hospital attached to Bangalore Medical College and Research Institute, Bengaluru. After obtaining clearance and approval from Institutional ethics committee (No. BMC/PGs/289/2016-17), 90 treatment naïve patients with T2DM attending Medicine Department fulfilling inclusion/exclusion criteria who gave Informed consent were included in the study.

The patients with T2DM were categorized into normal weight, overweight, and obese based on BMI criteria for Asians by the WHO. (Group 1-BMI 18.5–23.0 kg/m², Group 2-BMI >23.0–27.5 kg/m², and Group 3- BMI > 27.5 kg/m²).

Sample Size

30 patients with Type 2 diabetes were included for each group.

It was calculated using the formula: \( n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\pi_2 - \pi_1} \)

\( n = \) Sample size, \( 1 - \alpha/2 = \) The study with 95% confidence interval = 1.96, \( 1 - \beta = \) Power of the study as 80% = 0.84, \( \sigma^2 = \) Standard deviation = 0.62, \( \pi_2 - \pi_1 = \) difference between the two means = 0.48. Substituting the above readings to the formula the sample size is 26 for each group, but it was decided to include 30 per group for better evaluation.

Inclusion Criteria

The patients fulfilling the following criteria were included in the study:
1. Patients willing to give the informed consent
2. Patients aged ≥18 years of either sex
3. Newly diagnosed T2DM patients as per American Diabetic association guidelines
4. Patients with BMI > 18.5 kg/m².

Exclusion Criteria

The patients with following criteria were excluded from the study:
1. Newly diagnosed T2DM patients with glycosylated haemoglobin (HbA₁c) >9.0, fasting blood sugar (FBS) >180 mg/dl, postprandial blood sugar (PPBS) > 280 mg/dl
2. Patients suffering and on treatment for any other co-existing medical illness
3. Patient already on anti-diabetic medication
4. Pregnant and lactating mothers.

Methodology

All patients in three groups received starting dose of Tab. Metformin 500 mg bid, to be escalated by 500 mg fortnightly after checking FBS, up to a maximum of 1000 mg bid. All three groups were advised diet and exercise.

Demographic data, medical history, comorbid conditions, physical examination, lab investigations data with special emphasis pertaining to HbA₁c, FBS, PPBS, BMI, and details of drug prescription by the treating physician were recorded in the study proforma.

Baseline HbA₁c, FBS, and PPBS were done, BMI was measured at baseline. At the end of 2nd, 4th, 8th, and 12th weeks patient was followed up for FBS, PPBS, drug compliance, weight reduction/BMI, general evaluation, and adverse events. At the end of 16th week HbA₁c, FBS, and PPBS were done, BMI was measured and study terminated.

Assessment Tools

1. Efficacy was assessed by
   a. The percentage reduction in FBS, PPBS, HbA₁c, and BMI
   b. Attainment of glycemic targets as per ADA guidelines.
2. Safety was assessed by monitoring and recording adverse events reported by the patient at any time of the study.

Statistical Analysis

Data were collected and continuous variables were expressed as mean±SD (parametric data) or as median and inter quartile range (non-parametric data). The continuous data in this study were analyzed using repeated measure analysis of variance (ANOVA) for intra group comparison and ANOVA and paired t-test (parametric data) for intergroup comparison. Categorical data were expressed as percentages/proportions and were analyzed using Chi-square test. \( P < 0.05 \) was considered statistically significant. Statistical analysis was performed using VassarStats.
RESULTS

In the present study, 90 newly detected diabetic patients were enrolled according to inclusion and exclusion criteria into three groups in 1:1:1 ratio according to baseline BMI as normal weight (BMI 18.5 – ≤23); over weight (BMI ≥ 23–27.5); and obese (BMI >27.5). The participant flow diagram is depicted in Figure 1.

Baseline demographic characteristics

Majority of the patients (56.66%) belonged to the age group of 41–50 years. There were 52% males and 48% females altogether in the three groups. The baseline demographic characteristics in all three groups were matched as described elaborately in Table 1.

Baseline glycemic parameters

The baseline glycemic parameters such as FBS, PPBS, and HbA1c in three groups were matched as depicted in Table 2.

Efficacy measurements

Fasting blood glucose (FBS)

There was decrease in FBS levels in all three groups from baseline to end of 16 weeks, with no difference between the groups at the end of 16 weeks ($P = 0.74$). The significance values were based on ANOVA and the results are tabulated in Table 3 and depicted in Figure 2.

Post prandial blood glucose (PPBS)

There was decrease in PPBS levels in all three groups from baseline to end of 16 weeks, with no difference between the groups at the end of 16 weeks ($P = 0.05$). The significance values were based on ANOVA and the results are tabulated in Table 3 and depicted in Figure 3.

HbA1c

There was a decrease in the Mean HbA1c levels in all three groups from baseline to end of 16 weeks with no difference between the groups ($P = 0.04$). The significance values were based on ANOVA and the results are tabulated in Table 3 as well as depicted in the Figure 4.

Mean FBS, PPBS, and HbA1c reduction within normal weight, overweight, obese groups at follow-up visits from baseline to 4 weeks, 8 weeks, 12 weeks, and 16 weeks is shown in detail in Table 3. When comparing the values of glycemic parameters at 16th week with the baseline, it showed statistically significant reduction in the values of FBS, PPBS, and HbA1c ($P \leq 0.001$) in all the three groups.

Weight reduction

There was a statistically significant difference in weight reduction in overweight and obese groups from baseline to 16 weeks ($P < 0.001$) but no difference seen among normal weight group ($P = 0.91$). The results are tabulated in Table 4.
Adverse events

No serious adverse events were reported during treatment in all three groups. Out of 90 patients, total 10 patients experienced adverse events however, no statistically significant difference was noted among groups ($P = 0.63$). Headache, gastritis, nausea, etc., were the reported adverse events [Table 5]. These adverse events were mild in intensity. None of patients discontinued therapy due to adverse events. Metformin was well tolerated.

DISCUSSION

In the present study, the mean age among normal weight, over weight, and obese patients were 48.26 ± 1.12, 48.8 ± 0.85, and 45.46 ± 1.08 years, respectively, with majority of the patients in the age group of 41–50 years. This may be because T2DM is more prevalent past middle age. The male to female ratio in present study was 47:43. There was no statistically significant difference was seen among groups in terms of gender. According to IDF, the prevalence of diabetes for women is estimated to be 8.4% which is slightly lower than among men (9.1%).[3] However, gender was not expected to have an impact on efficacy, according to previous studies.[7] There were 1/3rd of patients had family history of DM among study participants. T2DM has a strong genetic component. Individuals with a parent with T2DM have an increased risk of diabetes; if both parents have T2DM, the risk is nearly 40%.[8]

In our study, we found out that Mean FBS reduction from baseline to week 16 was significant among all three groups 26 mg/dl, 25 mg/dl, and 28 mg/dl ($P<0.001$), but

| Glycemic parameter | Normal weight (mean ±SD) | Over weight (mean ±SD) | Obese (mean ±SD) | $P$-value
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<tr>
<td>FBS (mg/dl)</td>
<td>155.06±13.33</td>
<td>156.06±11.98</td>
<td>157.13±13.54</td>
<td>0.83</td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td>220.7±32.08</td>
<td>232.06±23.93</td>
<td>227.22±24.41</td>
<td>0.25</td>
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<tr>
<td>HbA$_{1c}$</td>
<td>7.55±0.39</td>
<td>7.56±0.43</td>
<td>7.74±0.59</td>
<td>0.23</td>
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Data analysis of within the group done by *repeated measure ANOVA, *paired t-test, shown significant change between the intervals in the group. Between group significance was based on ANOVA, $P<0.05$ is considered statistically significant
there was no significant difference between the groups (\( P = 0.74 \)). These findings are in consensus with the study conducted by Linong et al.,[7] who found out that fasting plasma glucose levels decreased similarly at the end of week 16 in all three groups (36 mg/dl, 39 mg/dl, and 38 mg/dl \( P = 0.46 \)) with metformin monotherapy. Similarly a study done by Deferenzo et al.[9] found out that the decline in fasting glucose was of similar magnitude in the obese (11.4 ± 0.8–8.9 ± 0.7 mmol/L) and normal weight (11.4 ± 0.8–8.7 ±0.7 mmol/L) diabetic individuals \( P < 0.01 \). The beneficial effects of the metformin to lower the fasting plasma glucose concentration are indirectly due to suppression of hepatic glucose output which is not related to BMI.

In the present study, we found out that Mean HbA\(_1c\) reduction from baseline to week 16 was significant among all three groups 0.91%, 0.82%, and 0.99% \( P < 0.001 \), but there was no significant difference from baseline to 16 weeks between the groups \( P > 0.05 \). In our study, 83% in normal weight, 77% and 67% in overweight and obese patients achieved target glycemic control of HbA\(_1c\). Below mentioned study results are in consensus with our study.

A prospective study conducted by Linong et al.[7] found out that at the end of week 16 with metformin monotherapy, HbA\(_1c\) levels decreased by –1.84%, –1.78%, and –1.78% in normal-weight, overweight, and obese diabetic patients, respectively, \( P = 0.6644 \). A database analysis by Cynthia et al.,[11] at a referral center Sydney, involving 1072 T2DM patients with monotherapy as metformin revealed that there was no difference in the reduction of A1C level between the groups during follow-up \( P = 0.7 \). Donnelly et al.[12] analyzed the database of 2064 treatment-naive T2DM patients at a diabetic research hospital at Scotland and by linear regression analysis found out that the HbA\(_1c\) reduction in non-obese patients was similar to that in obese patients (1.46% vs. 1.34%, \( P = 0.11 \)). Hence, studies conclude that BMI does not appear to influence treatment response to Metformin therapy.

HbA\(_1c\) is a good predictor of response to treatment for Metformin or any oral hypoglycemic agent. For every percentage point decrease in HbA\(_1c\), there was an associated 37% reduction in risk of microvascular complications.[10] The ADA guidelines for glycemic control recommend a target level of HbA\(_1c\) ≤7% to reduce the risk of micro- and macro-vascular complications.[13] Metformin is an oral anti-diabetic agent with highest reduction of HbA\(_1c\) 1–2%. A systematic review and meta-analyses by Cochrane concluded that Metformin had more benefit on reduction of HbA\(_1c\) (1.06%) when compared to other oral hypoglycemic agents.[14,15] Overall the findings from our prospective study are in consensus with those of the previous studies which concluded that glycemic response to Metformin monotherapy was similar among normal weight, overweight, and obese patients with T2DM.[16]

In the present study, body weight decreased slightly (0.3 Kg) in normal weight group at week 16. However, there is significant difference in the percentage weight reduction in overweight and obese group from baseline to 16 weeks. Furthermore, there is significant difference between the three groups \( P < 0.001 \). Similar study by Linong et al.[7] found out body weight decreased by 2.4%, 3.9%, and 3.5%, respectively. A database analysis by Cynthia et al.[11] showed that obese lost more weight during the follow-up than the non-obese.
The mechanisms by which metformin contributes to weight loss can be explained through the reduction in gastrointestinal absorption of carbohydrates, reduction of leptin and ghrelin levels after glucose overload, also by induction of a lipolytic and anorectic effect by acting on glucagon like peptide 1.

In the present study, we encountered mild adverse effects in all three groups. Gastrointestinal disturbances and headache were most common adverse effects seen. None of the patients discontinued metformin monotherapy because of side effects. Even in the previous similar studies Metformin was well tolerated with no serious adverse effects. However, minor adverse effects such as nausea, flatulence, diarrhea, and on long-term basis Vit. B12 deficiency were commonly encountered with Metformin therapy.

Our study had some limitations. Patients were recruited from single tertiary care hospital but a multicenter study with larger sample size would be the ideal. Further long-term, multicenter trials are required to accurately evaluate these effects.

**Strength and Limitations**

Robust statistical tests were employed which enabled us to generate valuable information and our study could provide reliable baseline information for future research. However, our study had some limitations. Patients were recruited from a single tertiary care hospital but a multicenter study with a larger sample size would be ideal. Furthermore, double blind, randomized control trials are required to accurately evaluate the long-term effects of metformin monotherapy in obese versus lean diabetics.

**CONCLUSION**

Metformin in normal weight group was found to be as efficacious as that of overweight and obese group for treating newly detected T2DM. Furthermore, the weight loss in Normal weight group is negligible compared to overweight and obese group patients. Hence, Metformin can be used as monotherapy for newly diagnosed, normal weight T2DM patients.

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**REFERENCES**


