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Original Research Article

A prospective, randomized, open-label study to compare the efficacy and safety of metformin versus metformin and fluoxetine in patients of type 2 diabetes mellitus with mild depression

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) and depression often occur together, increasing morbidity and mortality. While metformin shows potential antidepressant effects, its comparative efficacy and safety versus metformin-fluoxetine (MF) combination in T2DM patients with mild depression required further study.
Methods: This prospective, randomized, open-label study involved 60 patients (18-65 years) with T2DM and mild depression (HDRS 8-13) over 90 days. Group A received metformin 500 mg twice daily (n=30), while group B received metformin 500 mg twice daily plus fluoxetine 40 mg daily (n=30). Primary outcomes included glycemic parameters (FPG, HbA1c) and depression scores (HDRS, CGI). Safety, quality of life, and compliance were also assessed.
Results: Baseline parameters were comparable between groups. Both groups showed highly significant improvements ($p<0.001$) in glycemic control and depression scores. Over 60 days, group A showed 20% HDRS improvement versus group B's 10%; CGI-I was 3.33% in A versus 0% in B. By 90 days, HDRS improvement was 100% in group A versus 93.33% in B, while CGI-S and CGI-I improvements were 100% for both groups. No significant intergroup differences were observed for efficacy ($p>0.05$). Expected adverse effects were lower with metformin (28.33%) versus fluoxetine therapy (66.67%), all mild. Both groups demonstrated highly significant ($p<0.001$) QOL improvement and good compliance (≥85%).
Conclusions: Both treatments effectively improved glycemic control and depression symptoms. Metformin monotherapy demonstrated comparable efficacy and safety to the combination therapy of metformin and fluoxetine for managing mild depression in T2DM patients.

Keywords: Glycemic, HDRS, CGI, Quality of life

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by elevated blood glucose levels, typically managed through lifestyle modifications and pharmacological interventions. Metformin, an oral hypoglycemic agent, is considered the first-line treatment according to American Diabetes Association (ADA) (2023) guidelines due to its established efficacy and safety profile.[1]

Depression represents a significant psychiatric comorbidity in T2DM patients, with prevalence rates nearly twice as high as in the general population.[2] This bidirectional relationship creates a complex clinical scenario where depression can increase T2DM risk, while diabetes increases depression incidence, ultimately leading to higher morbidity and mortality, reduced treatment adherence, and diminished quality of life.

The management of depression in diabetic patients traditionally involves psychosocial interventions such as

cognitive behavioral therapy (CBT) and pharmacological treatments, primarily selective serotonin reuptake inhibitors (SSRIs) like fluoxetine. However, emerging evidence suggests that metformin may possess antidepressant properties beyond its glucose-lowering effects.

Recent studies have explored metformin's potential neuropsychiatric benefits. Guo et al demonstrated that metformin improved cognitive function and significantly reduced Montgomery-Åsberg depression rating scale (MADRS) and Hamilton rating scale for depression (HDRS) scores in T2DM patients with depression.[3] Animal studies have further suggested that combining metformin with fluoxetine might enhance antidepressant effects compared to monotherapy.[4]

Despite this emerging evidence, a significant research gap exists regarding the comparative effectiveness of metformin monotherapy versus combination therapy with fluoxetine in T2DM patients with mild depression. Notably, no human studies comparing these treatment strategies in the North Indian population have been identified in the literature.

This study aimed to address this research gap by comparing the efficacy and safety of metformin alone versus metformin combined with fluoxetine in patients diagnosed with T2DM and concomitant mild depression, with particular focus on glycemic parameters, depression severity, safety profile, and quality of life outcomes.

Aims and objectives

Primary objective was to compare the efficacy of metformin versus metformin and fluoxetine in patients of type 2 diabetes mellitus with mild depression. Secondary objective was to analyse the safety of the drugs. To assess the quality of life.

METHODS

Study design and place

It was a prospective, interventional, randomized, open-label, parallel-group comparative study. This study took place at the department of pharmacology and department of medicine, Government Medical College, Amritsar, Punjab, India.

Study population

Diagnosed cases of T2DM with concomitant mild depression according to International Classification of Diseases 11th Revision (ICD-11).

Study duration

This study took place for a period of 90 days.

Sample Size

This study included n=60 patients in group A and B (30 in each group).

Inclusion criteria

Diagnosed T2DM based on ADA 2023 guidelines (HbA1c≥6.5%, FPG≥126 mg/dl, 2-hour plasma glucose ≥200 mg/dL during OGTT, or random plasma glucose ≥200 mg/dl with classic symptoms). Concomitant mild depression according to ICD-11 criteria (category 6A70) with HDRS score 8-13. Age 18-65 years, either sex. Metformin and fluoxetine-naïve patients. Willingness to participate and provide informed consent.

Exclusion criteria

Unwillingness to provide consent. Type 1 DM, diabetes insipidus, or secondary causes of diabetes. Organic causes of depression or other psychiatric comorbidities. Cardiovascular, renal (GFR <30 ml/minute/1.73 m^2), or hepatic diseases. Use of medications potentially interacting with study drugs.

Before starting the study, ethical approval was obtained from the institutional ethics committee, Government Medical College, Amritsar (ethical clearance certificate number: IEC/GMCAMRITSAR/318/D-26/2022 batch), and the study was registered with Clinical Trial Registry of India (CTRI/2024/03/064215). A written informed consent was taken from all the patients prior to enrolment and after explaining the study particulars in easily understandable vernacular language.

Sample size calculation

Minimum sample size to be taken in each group, calculated by a formula using mean and standard deviation values from previous studies, was n=12.

Randomization and interventions

Patients were randomly allocated using simple randomization technique with computer software (random allocation software) into 2 groups of equal distribution, consisting of 30 patients each (after considering the total dropouts which were 2).

Group A (n=30): metformin 500 mg twice daily after meals. Group B (n=30): metformin 500 mg twice daily after meals + fluoxetine 40 mg once daily. Treatment duration was 90 days (12 weeks).

Outcome measures

Primary efficacy parameters

Glycemic control: fasting plasma glucose (FPG), random plasma glucose (RPG), 2-hour OGTT, HbA1c.

Depression assessment: Hamilton depression rating scale (HDRS), Clinical global impression scale (CGI-severity and CGI-improvement).

Secondary parameters

Lipid profile (total cholesterol, triglycerides, LDL-c, HDL-c), quality of life (visual analogue scale), patient compliance (pill count method).

Safety parameters

Adverse event monitoring, Complete blood count, liver function tests (AST, ALT, bilirubin, albumin, alkaline phosphatase), renal function tests (serum creatinine, blood urea).

Glycemic parameters, lipid profile, CBC, LFTs and RFTs were assessed at baseline and followed up at 30, 60 and 90 days.

Depression scales were assessed at baseline and followed up at 15, 30, 45, 60, 75, and 90 days. Adverse event monitoring and Compliance were assessed at 15, 30, 45, 60, 75, and 90 days

Statistical analysis

Statistical analysis was performed using SPSS software version 23.0. Quantitative data were expressed as mean±SD, with median (range) for HDRS and CGI scores. Intragroup changes were analysed using paired t-test for continuous data and Wilcoxon signed-rank test for depression scores and intergroup comparisons utilized unpaired t-test and Mann-Whitney U test respectively. A p value <0.05 was considered statistically significant, with p<0.001 considered highly significant.

RESULTS

Patient demographics and baseline characteristics

Sixty-two patients were initially enrolled, with one dropout in each group (group A: reluctance to follow up; group B: abdominal pain), resulting in 30 patients completing the study in each group.

Table 1: A comparison of 'baseline characteristics' between group 'A' and group 'B'.

Parameters	Group A (mean±SD)	Group B (mean±SD)	P value
Age (in years)	57.83±5.73	57.53±5.66	0.84
Weight (kg)	79.74±8.59	80.65±9.61	0.70
Height (cm)	164.98±8.08	164.90±6.88	0.97
BMI (kg/m^2)	29.19±2.48	29.59±3.16	0.59
Complete blood count			
Hemoglobin (gm/dl)	12.18±1.19	12.93±1.53	0.06
TLC (thousand/mm^3)	6456.47±1359.77	6589.73±1637.03	0.73
Glycemic			
Fasting plasma glucose (mg/dl)	174.50±26.55	167.97±26.72	0.35
HbA1c (%)	8.37±0.74	8.31±0.88	0.79
Depression scales			
HDRS [median (range)]	10 (9,13)	12 (9,13)	0.17
CGI-s [median (range)]	3 (2,4)	3 (2,4)	0.86
Lipid			
Total cholesterol (mg/dl)	195.30±49.44	193.10±41.74	0.9931
Serum triglycerides (mg/dl)	156.51±31.83	146.05±34.83	0.45
HDL-c (mg/dl)	51.90±9.67	53.47±11.69	0.1355
LDL-c (mg/dl)	148.67±31.83	142.48±39.73	0.73
Hepatic			
AST (IU/l)	25.67±8.53	25.77±9.73	0.97
ALT (IU/l)	25.56±6.67	26.58±11.44	0.68
Renal			
Serum creatinine (mg/dl)	0.96±0.23	0.95±0.21	0.88
Blood urea (mg/dl)	22.77±6.82	23.10±7.31	0.85
VAS (QOL)	69.17±5.27	69.83±6.22	0.66

BMI- body mass index, TLC- total leucocyte count, HDRS- Hamilton depression rating scale, CGI- clinical global impressions, CGI-s- severity, AST- aspartate aminotransferase, ALT- alanine aminotransferase, HDL- high density lipoproteins, LDL- low-density lipoproteins, C- cholesterol, VAS- visual analogue scale, QOL- quality of life. p>0.05: Not significant *p<0.05: significant; **p<0.001: highly significant (p value: Unpaired t-test).

Table 2: A comparison of mean percentage change in parameters of patients between group 'A' and group 'B' over '90' days of treatment.

Parameters	Group A (Mean % change ±SD)	Group B (Mean % change ±SD)	P value
FPG	19.40±12.67	17.90±14.60	0.67
HbA1c	15.07±10.18	13.57±7.46	0.52
Hemoglobin	4.47±5.88	2.91±8.44	0.41
TLC	0.44±21.26	1.62±19.44	0.70
Total cholesterol	12.07±10.16	6.61±11.28	0.06
Serum triglycerides	14.33±10.89	8.81±18.12	0.16
HDL-c	17.51±11.15	19.42±15.16	0.58
LDL-c	15.56±12.14	9.92±16.60	0.09
VAS	31.03±7.22	25.17±3.87	0.13

p>0.05: not significant *p<0.05: significant; **p<0.001: highly significant (p value: unpaired t-test).

Table 3: A comparison of percent improvement in HDRS scale between group 'A' and group 'B' over '90' days of treatment.

Over (days)	HDRS						P value
	Group A			Group B			
	Median (range)	N (%) (score= 0-7)	N (%) (score= 8-13)	Median (range)	N (%) (score= 0-7)	N (%) (score= 8-13)	
0	10 (9,13)	-	30 (100)	12 (9,13)	-	30 (100)	0.17
15	10 (8,13)	-	30 (100)	12 (9,12)	-	30 (100)	0.27
30	9 (8,12)	-	30 (100)	12 (8,12)	-	30 (100)	0.17
45	8 (7,11)	-	30 (100)	11 (8,12)	-	30 (100)	0.16
60	8 (7,10)	6 (20)	24 (80)	9.5 (8,11)	3 (10)	27 (90)	0.08
75	7 (6,9)	17 (56.67)	13 (43.33)	8 (6,9)	14 (46.67)	16 (53.33)	0.29
90	7 (5,7)	30 (100)	-	7 (5,7)	28 (93.33)	2 (6.67)	0.58

p>0.05: not significant *p<0.05: significant; **p<0.001: highly significant (p value: Mann-Whitney U test).

Table 4: A comparison of percent improvement in CGI-I scales between group 'A' and group 'B' over 90 days of treatment.

Over (days)	CGI-I scores										P value
	Group A					Group B					
	Median (range)	N (%)				Median (range)	N (%)				
		4	3	2	1		4	3	2	1	
15	4 (3,4)	26 (86.67)	4 (13.33)	-	-	4 (3,4)	21 (70)	9 (30)	-	-	
30	4 (3,4)	18 (60)	12 (40)	-	-	3 (3,4)	11 (36.67)	19 (63.33)	-	-	0.07
45	3 (2,3)	-	25 (83.33)	5 (16.67)	-	3 (2,3)	-	20 (66.67)	10 (33.33)	-	0.14
60	2 (1,3)	-	10 (33.33)	19 (63.33)	1 (3.33)	2 (2,3)	-	5 (16.67)	25 (83.33)	-	0.23
75	2 (1,2)	-	-	18 (60)	12 (40)	1 (1,2)	-	-	12 (40)	18 (60)	0.13
90	1 (1,1)	-	-	-	30 (100)	1 (1,1)	-	-	-	30 (100)	0.73

p>0.05: not significant *p<0.05: significant; **p<0.001: highly significant (p value: Mann-Whitney U test).

Baseline characteristics (Table 1) were comparable between groups (p>0.05). It was observed that the prevalence of T2DM with depression increased with the increasing age (13.33% in age 45-50 years, 21.67% in age 51-55 years, 23.33% in age 56-60 years and 41.67% in age 61-65 years). Mean age was 57.83±5.66 years in group A

and 57.53±5.66 years in group B. Gender distribution showed 10 females and 20 males in group A, compared to 17 females and 13 males in group B. All patients had mild depression according to HDRS scale (score 8-13) at baseline.

Efficacy outcomes

Glycemic control

Both groups demonstrated highly significant improvements in all glycemic parameters from baseline to day 90 ($p<0.001$). Mean HbA1c decreased from 8.37±0.74% to 6.32±0.71% in group A and from 8.31±0.88% to 6.45±0.71% in group B. Similar significant reductions were observed in FPG, RPG, and 2-hour OGTT values (Table 2).

Intergroup comparison revealed no statistically significant differences in mean percentage change of glycemic parameters between treatments ($p>0.05$), indicating comparable efficacy in diabetes management.

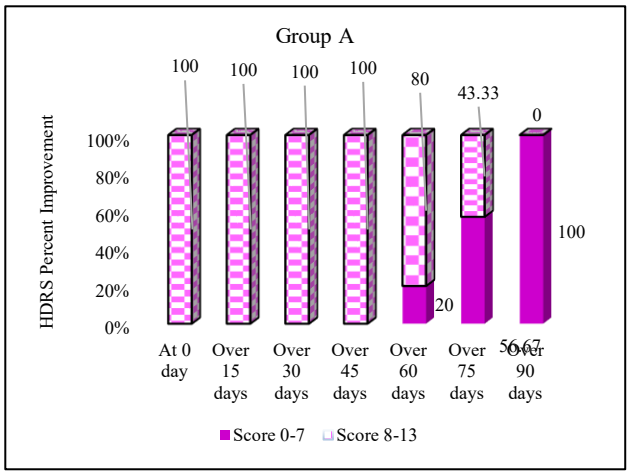

Figure 1: Intragroup comparison of improvement in HDRS scale in group 'A' over '90' days of treatment.

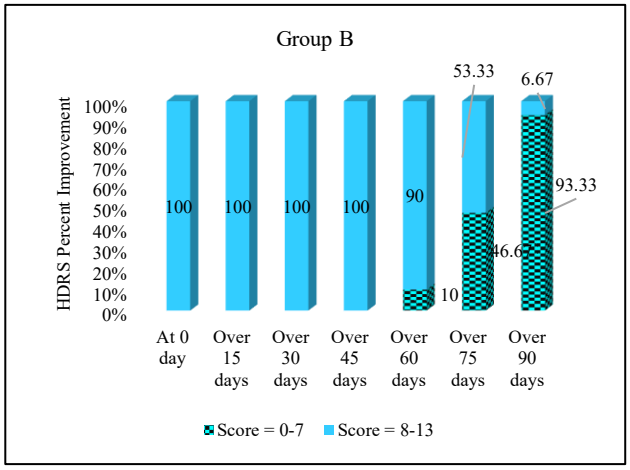

Figure 2: Intragroup comparison of improvement in HDRS scale in group 'B' over '90' days of treatment.

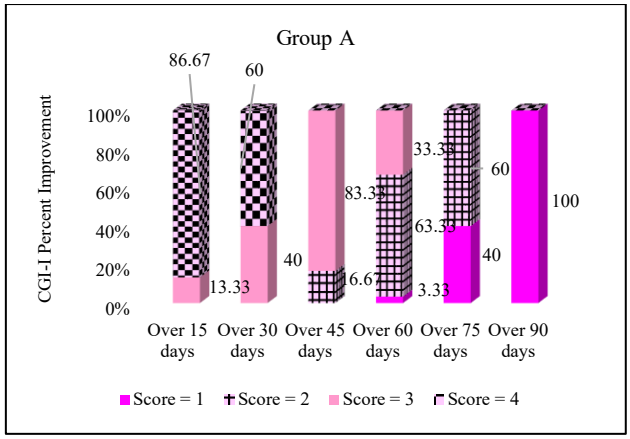

Figure 3: Intragroup comparison of improvement in CGI-I scale in group 'A' over '90' days of treatment.

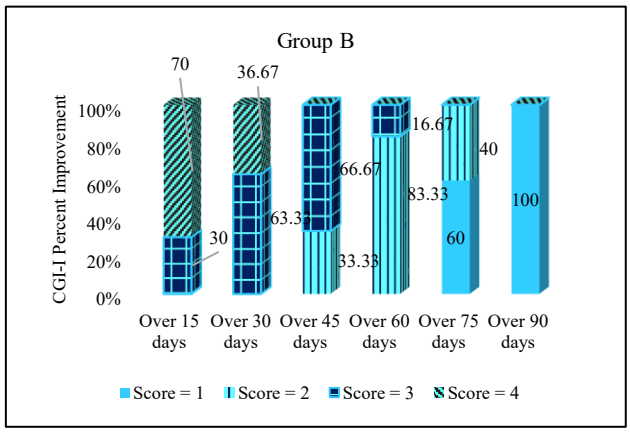

Figure 4: Intragroup comparison of improvement in CGI-I scale in group 'B' over '90' days of treatment.

Depression outcomes

Both groups showed highly significant reduction in depression scores ($p<0.001$). By day 60, 20% of patients in group A achieved symptom-free status according to HDRS scale, compared to 10% in group B, though on intergroup comparison, this difference was not statistically significant. By day 90, 100% of patients in group A achieved symptom-free status according to HDRS scale, compared to 93.33% in group B (Figures 1-4).

Median HDRS and CGI scores improved significantly within each group and no statistically significant intergroup differences ($p>0.05$) (Tables 3 and 4), suggesting comparable antidepressant efficacy were observed.

Lipid profile

Significant improvements in lipid parameters were observed in both groups ($p<0.001$), including reductions in total cholesterol, triglycerides, and LDL-c, with increases in HDL-c. No significant intergroup differences were found ($p>0.05$) (Table 2).

Table 5: A comparison of expected adverse effect profile of patients between group 'A' and group 'B' over '90' days of treatment on hepatic and renal parameters.

Parameters	Group A (Mean % change ±SD)	Group B (Mean % change ±SD)	P value
Hepatic			
AST	3.36±29.53	12.12±32.85	0.28
ALT	3.74±20.60	11.88±36.49	0.15
Serum bilirubin	8.78±31.82	5.56±55.54	0.22
Albumin	6.49±10.80	4.24±14.14	0.48
Alkaline phosphatase	0.75±18.57	0.03±22.12	0.88
Renal			
Serum creatinine	12.51±35.45	8.02±23.54	0.56
Blood urea	0.41±18.04	6.39±19.94	0.23

p>0.05: not significant *p<0.05: significant; **p<0.001: highly significant (p value: unpaired t-test).

Safety and tolerability

Both treatments were well tolerated with no serious adverse events requiring discontinuation, except for one dropout in group B due to mild abdominal pain (Table 5). The percentage of adverse effects suspected due to metformin was 28.33%, while those suspected due to fluoxetine were 66.67% (Figure 5). All adverse effects were rated as mild in severity (done by Modified Hartwig and Siegel's severity assessment scale), with gastrointestinal symptoms being most common.

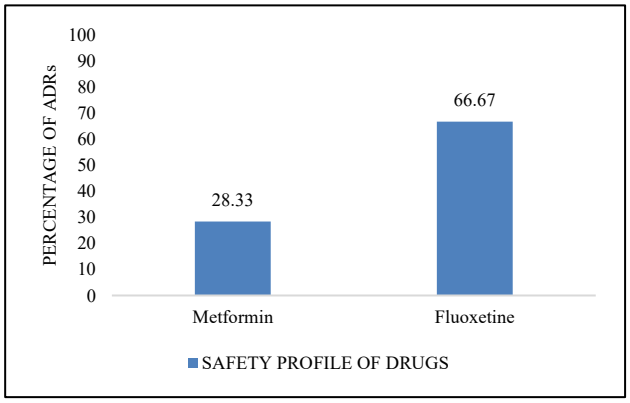

Figure 5: Comparison of expected adverse effect profile of patients in metformin verses fluoxetine groups over '90' days of treatment.

Laboratory parameters including complete blood count, liver function tests, and renal function tests remained within normal ranges throughout the study in both groups.

Quality of life and compliance

Both groups showed highly significant improvement in quality-of-life scores (p<0.001), with no significant intergroup difference (p=0.13) (Table 2). Patient compliance was consistently good (≥85%) in both groups throughout the study period, with no significant difference between treatments.

DISCUSSION

This prospective, comparative, randomised, open-label, parallel-group, interventional study evaluated the efficacy and safety of metformin alone versus metformin combined with fluoxetine in patients with T2DM and concomitant mild depression in the north Indian population.

Two patients dropped out of the study: one from group A due to reluctance to follow up, and one from group B due to an adverse event (abdominal pain). The demographic profile indicated a mean age in the 50-60-year range, with a slightly higher number of males compared to females overall, although the female prevalence in group B was higher. These demographic findings regarding age align with a study by Ravi et al in which prevalence was observed to be 53.2±11.23 years, and the gender distribution aligns with Miguel et al in which 48.10% were women and Ravi et al where 48.10% was female population.[5,6]

Glycemic parameters

Intragroup analysis demonstrated a highly significant reduction in mean glycemic parameters fasting plasma glucose (FPG), random plasma glucose (RPG), 2-hour oral glucose tolerance test (OGTT), and HbA1c) throughout the 90-day study period in both treatment groups (p<0.001). Specifically, at the end of 90 days, there was a highly significant reduction in FPG, RPG, 2 hour OGTT, and HbA1c in both group A and group B compared to baseline. This observed efficacy of metformin aligns with findings from a systematic review by Noel et al which stated metformin (1000 mg/day) is effective for long-term T2DM control, a trial by Manuela et al showed significant (p=0.004) HbA1c decrease with metformin (1000 mg/day) in 2 months, and a dose-ranging study by Alan reporting lowered FPG and HbA_1c with metformin (500-2000 mg) (p=0.02).[7-9] The significant improvement in FPG and HbA1c in group B (receiving fluoxetine in addition to metformin) corresponds with a trial by Habibolah Khazaie et al where fluoxetine (40 mg) and citalopram (40 mg)

showed significant improvement (p<0.001) in FPG and HbA1c in T2DM patients with depression over 12 weeks.[10]

Intergroup comparison of the mean percentage change in glycemic parameters over 90 days showed no statistically significant difference between group A (metformin alone) and group B (metformin + fluoxetine). While studies have explored the effect of fluoxetine alone or in combination with other agents on glycemic control, the sources note a lack of human studies specifically examining the combination of metformin and fluoxetine on glycemic parameters in T2DM with mild depression.

Depression scores

Intragroup analysis revealed a highly significant reduction in the median scores of HDRS, CGI-s, and CGI-i over the 90-day study period in both treatment groups (p<0.001). All patients, starting with mild depression according to HDRS (score 8-13), showed significant improvement from baseline by day 15 (p<0.05) and highly significant improvement over 90 days (p<0.001) on the HDRS scale. By the end of 90 days, the median scores for HDRS, CGI-s, and CGI-i indicated significant improvement in both groups. This significant improvement in depression scores with metformin alone aligns with studies by Yating et al and Guo et al which reported significant reductions in depression scores with metformin (500-2000 mg and 1000 mg respectively) treatment in T2DM patients (p<0.001 and p<0.001 respectively) over 24 weeks.[3,11] The improvement in depression scores in group B (metformin + fluoxetine) corresponds with trials by Habibolah et al and Lustman et al, which demonstrated significant reduction (p<0.001 and p=0.03 respectively) in depression severity with fluoxetine (40 mg) in diabetic patients with depression over 12 weeks.[10,12]

Intergroup comparison of depression scores over 90 days showed no statistically significant difference between group A and group B on the HDRS scale. Similarly, intergroup comparison of CGI-s and CGI-i scores also showed no statistically significant difference over 90 days. However, intragroup analysis showed earlier onset of improvement in depression scores with metformin alone, though this was not statistically significant in the intergroup comparison. The sources mention a lack of human studies comparing the efficacy and safety of metformin and fluoxetine together versus metformin alone in T2DM with concomitant mild depression. An animal study by Poggini et al suggested that a combination of fluoxetine (30 mg/kg) and metformin (200 mg/kg) improved behavioural phenotype more than either drug alone in a mouse model of depression (p<0.001) in 1-week of treatment, which differs from the findings of this human study's intergroup comparison over 90 days.[4]

Other parameters

Intragroup analysis of complete blood count (CBC) parameters (hemoglobin, TLC) showed no statistically significant changes over 90 days in either group, with values remaining in the normal range. This aligns with a retrospective study by Athanasios et al which found no significant effect of metformin (1000 mg/day) on CBC parameters in T2DM patients over 12 months (p=0.45).[13] Intergroup comparison of the mean percentage change in CBC parameters was also statistically non-significant.

Lipid parameters

Intragroup analysis showed a highly significant reduction in mean levels of total cholesterol, serum triglycerides, and LDL-c, and a highly significant increase in HDL-c levels over 90 days in both groups compared to baseline (p<0.001 for total cholesterol, HDL-c, LDL-c; p<0.05 for serum triglycerides). This positive impact on lipid profiles with metformin aligns with meta-analyses by Syed et al and Patel et al in 12 weeks which found significant improvements (p<0.001 and p<0.001 respectively) in lipid parameters with metformin (500-1000 gram and 500 mg respectively).[14,15] The significant reduction in triglycerides in group B (metformin + fluoxetine) is also in accordance with a meta-analysis by Ye et al regarding fluoxetine's (20-60 mg) metabolic effects (p<0.001).[16] Intergroup comparison of the mean percentage change in lipid parameters over 90 days was not statistically significant. Although a study by Manjarrez et al found significant improvements in lipid parameters (p<0.05) with a combination of metformin (1500 mg/day) and fluoxetine (20 mg/day) in patients with metabolic syndrome over 20 weeks, the sources noted no human studies specifically on the effect of this combination on lipid profile in T2DM with depression.[17]

Hepatic parameters

Intragroup analysis of hepatic parameters (AST, ALT, serum bilirubin, albumin, alkaline phosphatase) showed non-significant changes over 90 days in both groups, with all values remaining within the normal reference range. This suggests the treatments were well-tolerated regarding liver function. However, a meta-analysis by Jalali et al found a significant reduction (p<0.05) in AST but not ALT levels with metformin (1000 mg/day) in non-alcoholic liver disease patients, and a study by Feng et al reported significant reductions in AST and ALT levels (p<0.05) with metformin (750-2000 mg/day) in T2DM patients with NAFLD over 24 weeks, which differs from the present study's findings in the mild depression population.[18,19] Intergroup comparison of the mean percentage change in hepatic parameters was also statistically non-significant, and values remained in the normal range. The sources indicated no human studies were found evaluating the combination of metformin and fluoxetine on hepatic parameters in this population.

Renal parameters

Intragroup analysis showed a statistically significant reduction in mean serum creatinine levels over 90 days in

both groups ($p<0.001$ in group A, $p=0.015$ in group B). Mean blood urea levels showed non-significant changes in both groups. Renal parameters remained within the normal reference range throughout the study. The significant reduction in serum creatinine with metformin (1500 mg/day) aligns with a study by Zhang et al ($p<0.001$).[20] An animal study by Aksu et al also reported a significant decrease in serum creatinine with fluoxetine (20 mg/kg) ($p<0.05$).[21] Intergroup comparison of the mean percentage change in renal parameters over 90 days was statistically non-significant. The sources noted a lack of human studies on the effect of metformin in T2DM patients on renal parameters, and no human study on the combination of metformin and fluoxetine on renal parameters in this population.

Safety profile

Assessment of adverse effects indicated that both metformin and fluoxetine were generally well tolerated, with no serious adverse effects or need to discontinue treatment for most patients. The total percentage of suspected adverse reactions (ADRs) was 28.33% for metformin (across both groups) and 66.67% for fluoxetine (in group B). These ADRs typically had possible or probable causality and were assessed as level 1 (mild) severity using the Modified Hartwig and Siegel's Scale. Common expected ADRs with metformin included gastrointestinal disturbances like abdominal pain, metallic taste, nausea, tiredness, and vomiting. Expected ADRs with fluoxetine included nervous system effects like agitation, drowsiness, dry mouth, headache, and insomnia, as well as gastrointestinal issues like anorexia, diarrhoea, and nausea. These findings align with a meta-analysis by Nabrdalik et al which stated that gastrointestinal side effects of metformin (500-2000 mg/day) are common but tolerable.[22]

Quality of life (QOL)

Intragroup analysis showed a highly significant improvement in QOL as measured by the VAS scale over 90 days in both groups ($p<0.001$). This indicates improved quality of life after treatment administration. An intergroup comparison of the mean percentage change in VAS scores after 90 days was statistically non-significant. A prospective study by Ritu et al found statistically significant improvement ($p<0.001$) in Health-related QOL in T2DM patients receiving metformin (1000 mg/day), which supports the findings in group A of the present study.[23] The sources noted a lack of similar studies comparing the effects of the specific concomitant therapies evaluated here on the VAS score.

Patient compliance

Patient compliance, assessed by the pill count method, was good (≥ 85%) in both groups throughout the 90-day study period and decreased non-significantly over time in both groups. The mean compliance at 15 days and 90 days was comparable and statistically non-significant between the two groups. Good compliance supports the effectiveness observed in the study.

Clinical implications

These findings suggest that metformin monotherapy may represent a valuable first-line approach for T2DM patients with mild depression, potentially eliminating the need for additional antidepressant medication in some mild cases. This could reduce pill burden, minimize drug interactions, better safety and improve cost-effectiveness while maintaining therapeutic efficacy.

The results support a stepwise approach to managing depression in T2DM patients, beginning with optimization of metformin therapy before considering additional antidepressants, particularly in mild depression cases.

The study has several strengths, including being a novel study in an north Indian T2DM population with mild depression receiving metformin therapy. It is also noted as the first study found in the literature search to assess both HDRS and CGI scores, quality of life, and patient compliance in T2DM patients with mild depression receiving metformin therapy vs combination of metformin and fluoxetine.

Several limitations should be acknowledged. The relatively small sample size (n=60) and short study duration (90 days) limit the power to detect subtle differences and long-term effects. The single-centre, open-label design may introduce bias, particularly in subjective outcome measures. Additionally, the paucity of directly comparable studies in the literature limits our ability to contextualize these findings fully.

CONCLUSION

This study demonstrates that both group A and group B showed statistically significant improvement in glycemic parameters, depression scales and lipid parameters. Though metformin alone showed greater improvement in depression scores i.e. early onset of improvement of scores though statistically non-significant. These findings suggest that metformin monotherapy may offer a favourable safety profile for managing mild depression in T2DM patients, supporting its consideration as a first-line approach before adding antidepressant medications. The quality of life and compliance were comparable and optimum in both groups A and B.

The results have important implications for clinical practice, potentially simplifying treatment regimens while maintaining therapeutic effectiveness. Thus, the study suggests that the monotherapy of metformin maybe more efficacious and with a better safety profile as compared to the combination of metformin and fluoxetine in subset of patients of T2DM with mild depression.

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