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Evaluation of the Effectiveness of Metformin Therapy in Patients with Type 2 Diabetes Mellitus

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Abstract:

Diabetes mellitus is a major chronic metabolic disorder with growing global health complications.

This retrospective study aimed to evaluate the clinical effectiveness of metformin in patients with type 2 diabetes. Metformin primarily acts by inhibiting hepatic gluconeogenesis and activating the intracellular AMPK enzyme. A single-group pretest–posttest design was applied to the medical records of 50 patients with type 2 diabetes attending an endocrinology and diabetes clinic. Fasting blood glucose (FBG) and HbA1c were compared before and after at least three months of metformin therapy, and differences by gender and dose were examined using an independent-samples t-test and one-way ANOVA with Tukey's post hoc test. Glycemic indicators improved after therapy: the proportion of patients in the diabetic range fell from 82% to 14% for FBG and from 92% to 22% for HbA1c. Females showed a greater reduction in FBG than males (mean difference 9.3 mg/dL, 95% CI 1.2 to 17.4, $p = 0.025$), whereas the difference in HbA1c was not significant ($p = 0.236$). Higher metformin doses were associated with larger reductions in both indicators, the largest being in the 1000 mg group. Because the study had no control group, a small sample, and no adjustment for age, baseline glycemia, treatment duration or adherence, these findings should be interpreted as associations rather than proof of a causal effect.

Keywords:

Type 2 Diabetes Mellitus, Metformin Therapy, Glycemic Control, Fasting Blood Glucose, HbA1c, Gender Differences, Dose Response

1.1. Introduction to Diabetes Mellitus:

Diabetes mellitus is a chronic metabolic disease characterized by elevated levels of glucose in the blood resulting from defects in insulin secretion, insulin action, or both. Insulin is a hormone produced by the beta cells of the pancreas, and its primary function is to regulate blood glucose levels by facilitating the entry of glucose into body cells for energy production. When insulin production becomes insufficient or when body tissues become resistant to its action, glucose accumulates in the bloodstream, leading to hyperglycemia and multiple long-term complications affecting different organs of the body.

According to the World Health Organization, diabetes mellitus has become one of the fastest-growing global health problems due to unhealthy dietary habits, obesity, sedentary lifestyles, aging populations, and genetic predisposition. Persistent uncontrolled hyperglycemia may contribute to severe complications such as cardiovascular disease, kidney failure, blindness, neuropathy, and peripheral vascular

disease. Therefore, early diagnosis and effective management are essential for reducing morbidity and mortality associated with diabetes. Diabetes mellitus is generally classified into several major types. Type 1 diabetes mellitus results from autoimmune destruction of pancreatic beta cells, leading to absolute insulin deficiency. This type commonly develops during childhood or adolescence, and patients usually require lifelong insulin therapy. According to Atkinson et al. (2014), genetic susceptibility and environmental factors both contribute to the development of type 1 diabetes. Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and accounts for the majority of diabetic cases worldwide. It is characterized by insulin resistance combined with progressive pancreatic beta-cell dysfunction. In the early stages, the pancreas compensates by producing larger amounts of insulin, but over time insulin secretion becomes insufficient to maintain normal blood glucose levels. Researchers such as DeFronzo (2009) explained that obesity, physical inactivity, genetic factors, and unhealthy diets are major contributors to the development of type 2 diabetes.

Another form of diabetes is gestational diabetes mellitus, which occurs during pregnancy due to hormonal changes that impair insulin sensitivity. Although blood glucose levels often return to normal after delivery, affected women remain at increased risk of developing type 2 diabetes later in life. Additional less common forms of diabetes may result from genetic disorders, pancreatic diseases, hormonal abnormalities, or medication-induced hyperglycemia. The pathophysiology of diabetes involves disturbances in glucose metabolism and insulin activity. Under normal physiological conditions, insulin binds to receptors on muscle and adipose tissue cells, allowing glucose uptake from the bloodstream. Insulin also suppresses hepatic glucose production and promotes glycogen synthesis. In diabetic patients, impaired insulin secretion or insulin resistance disrupts these mechanisms, causing elevated blood glucose levels. Chronic hyperglycemia eventually damages blood vessels and organs through oxidative stress, inflammation, and metabolic dysfunction. The causes and risk factors associated with diabetes vary according to the type of disease. Family history and genetic predisposition play important roles in both type 1 and type 2 diabetes. Obesity, especially central obesity, is strongly associated with insulin resistance and represents one of the most significant risk factors for T2DM. Sedentary lifestyle, poor dietary habits, hypertension, dyslipidemia, smoking, and aging also increase the likelihood of developing diabetes. According to Hu et al. (2001), lifestyle modifications including regular physical activity and healthy nutrition significantly reduce the risk of type 2 diabetes among high-risk individuals. The treatment of diabetes focuses primarily on maintaining blood glucose levels within target ranges to prevent complications. Management strategies include lifestyle modifications, dietary regulation, physical exercise, weight control, and pharmacological therapy. Different antidiabetic medications act through various mechanisms to improve glycemic control depending on the underlying pathophysiology of the disease. Some antidiabetic drugs stimulate insulin secretion from pancreatic beta cells, such as sulfonylureas. Other medications improve insulin sensitivity, including metformin and thiazolidinediones. Metformin primarily reduces hepatic glucose production and enhances peripheral insulin sensitivity without causing significant hypoglycemia. According to Bailey and Day (2004), metformin remains one of the most widely used medications in type 2 diabetes management because of its efficacy and safety profile. Newer antidiabetic medications target additional physiological pathways involved in glucose regulation. Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) reduce blood glucose by increasing urinary glucose excretion through the kidneys. Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) stimulate insulin secretion, suppress glucagon release, delay gastric emptying, and promote weight loss. Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) prolong the activity of incretin hormones that regulate insulin secretion after meals. According to Inzucchi et al. (2015), these therapeutic advances have expanded treatment options for patients with type 2 diabetes and improved individualized care strategies. Because diabetes is a progressive chronic disease, treatment often requires continuous adjustment according to patient response, disease duration, comorbidities, and risk of complications. Physicians play a major role in selecting the most appropriate therapeutic approach for each patient while considering efficacy, safety, accessibility, cost, and patient adherence. Therefore, understanding diabetes pathophysiology and mechanisms of antidiabetic medications is essential before discussing physician perspectives on metformin and newer antidiabetic drugs in type 2 diabetes management.

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2. Structure & Mechanism of action, Clinical Uses, Side Effects, and Combination Therapy

Metformin is considered the cornerstone pharmacological treatment for Type 2 Diabetes Mellitus (T2DM) and remains the most frequently prescribed antidiabetic medication worldwide. It belongs to the biguanide class of drugs and has been recommended as first-line therapy by major international organizations including the American Diabetes Association and the European Association for the Study of Diabetes. Since its introduction into clinical practice, metformin has demonstrated substantial efficacy in controlling blood glucose levels while maintaining a favorable safety profile and relatively low cost compared with many newer antidiabetic agents (Nathan et al., 2009).

2.1. Chemical Structure of Metformin:

The chemical name of metformin is **1,1-Dimethylbiguanide hydrochloride**, and its molecular formula is **$C_4H_{11}N_5 \cdot HCl$**. The drug belongs to the biguanide family and has a simple chemical structure that contributes to its stability and effectiveness in glucose regulation. Researchers have extensively studied its molecular properties and pharmacological actions over several decades (Bailey & Day, 2004).

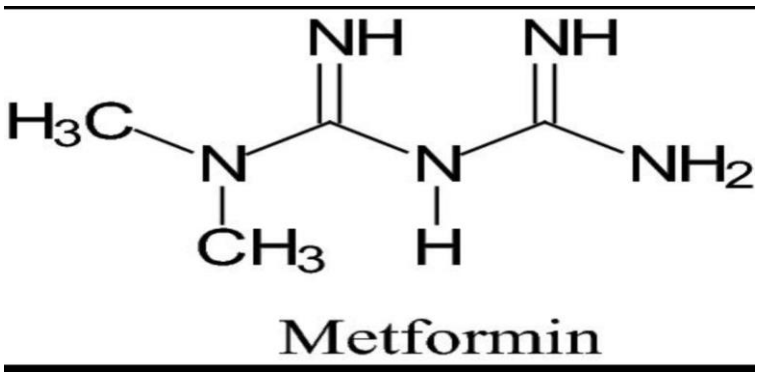


Figure 1. Chemical Structure of Metformin Hydrochloride

2.2 Mechanism of Action of Metformin:

Metformin lowers blood glucose levels through several physiological mechanisms without directly stimulating insulin secretion from pancreatic beta cells. One of its primary actions is the inhibition of hepatic gluconeogenesis, which reduces the amount of glucose produced by the liver and released into the bloodstream (Bailey & Day, 2004). In addition, metformin activates adenosine monophosphate-activated protein kinase (AMPK), an important intracellular enzyme responsible for regulating cellular energy balance. Activation of AMPK enhances insulin sensitivity, promotes glucose uptake by skeletal muscles, and decreases hepatic glucose production (Zhou et al., 2001).

Another important mechanism involves reducing intestinal glucose absorption, which limits the amount of glucose entering circulation after meals. Furthermore, metformin improves peripheral glucose utilization and decreases insulin resistance in muscle and adipose tissues (DeFronzo et al., 2016).

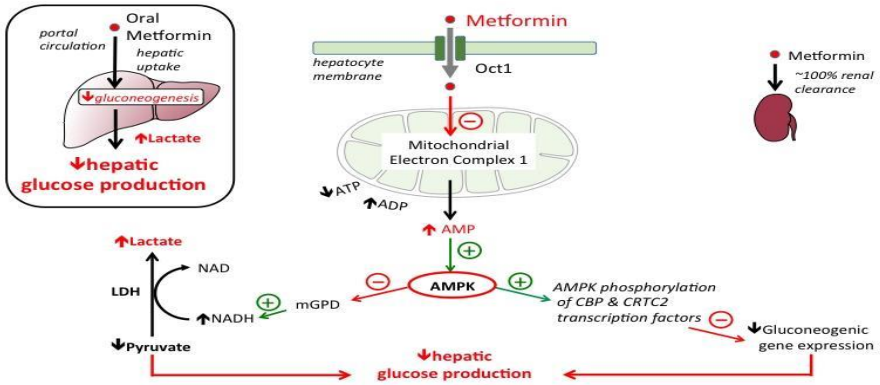


Figure (2). Mechanism of metformin

Unlike sulfonylureas, metformin rarely causes hypoglycemia because it does not increase endogenous insulin secretion. This characteristic has contributed significantly to its widespread acceptance among physicians and patients (Nathan et al., 2009). Several clinical studies have shown that metformin can reduce glycated hemoglobin (HbA1c) by approximately 1–2%, making it highly effective as an initial therapy for patients with newly diagnosed type 2 diabetes (UK Prospective Diabetes Study Group, 1998).

2.3. Clinical Uses of Metformin Beyond Diabetes:

Although metformin is primarily prescribed for type 2 diabetes mellitus, it has several additional therapeutic applications.

a) Polycystic Ovary Syndrome (PCOS):

Metformin is widely used in women with polycystic ovary syndrome because insulin resistance is a major component of the disorder. By improving insulin sensitivity, metformin may restore ovulation, improve menstrual regularity, and increase fertility rates among affected women (Lord et al., 2003).

b) Prediabetes:

Patients with prediabetes often receive metformin as part of preventive treatment strategies. Research conducted by the Diabetes Prevention Program Research Group (2002) demonstrated that metformin significantly reduced the progression from prediabetes to type 2 diabetes in high-risk individuals.

c) Obesity and Weight Management:

Metformin has also been investigated for weight management because it may contribute to modest reductions in body weight through improvements in insulin sensitivity and appetite regulation (Knowler et al., 2002).

d) Metabolic Syndrome:

Patients with metabolic syndrome may benefit from metformin therapy due to its positive effects on insulin resistance, blood glucose regulation, and cardiovascular risk factors (Reaven, 2005).

e) Non-Alcoholic Fatty Liver Disease (NAFLD):

Metformin has been evaluated as a potential treatment for non-alcoholic fatty liver disease because insulin resistance plays a central role in the development of hepatic steatosis. Studies have suggested that metformin may improve liver enzyme levels and metabolic outcomes in selected patients (Marchesini et al., 2001).

2.4. Side Effects of Metformin:

Metformin is generally considered safe and well tolerated; however, several adverse effects have been documented.

- **Gastrointestinal Side Effects:**
  The most commonly reported side effects involve the gastrointestinal system. These include nausea, vomiting, diarrhea, abdominal discomfort, bloating, and loss of appetite. Such symptoms are particularly common during the initial stages of therapy and often improve with continued use or gradual dose escalation (Dujic et al., 2016).
  Some patients also report experiencing a metallic taste in the mouth, which may affect medication adherence during early treatment (Bailey & Turner, 1996).
- **Vitamin B12 Deficiency**:
  Long-term metformin therapy may interfere with vitamin B12 absorption, increasing the risk of deficiency and associated neurological complications. Therefore, physicians may recommend periodic monitoring of vitamin B12 levels in patients receiving prolonged treatment (de Jager et al., 2010).
- **Lactic Acidosis**:
  Although rare, lactic acidosis is considered the most serious adverse effect associated with metformin use. The condition is more likely to occur in patients with severe renal impairment, advanced liver disease, heart failure, or conditions causing tissue hypoxia (Salpeter et al., 2010).

2.5. Antidiabetic Medications Commonly Combined with Metformin:

Because type 2 diabetes is a progressive disease, many patients eventually require combination therapy to achieve adequate glycemic control.

a) **Sulfonylureas**:
   Sulfonylureas such as glimepiride, gliclazide, and glyburide are frequently combined with metformin. These medications stimulate pancreatic insulin secretion and complement the insulin-sensitizing effects of metformin (Inzucchi et al., 2015).

b) **DPP-4 Inhibitors**:
   DPP-4 inhibitors including sitagliptin, saxagliptin, linagliptin, and vildagliptin are commonly prescribed alongside metformin because they enhance incretin hormone activity and improve postprandial glucose control (Deacon, 2011).

c) **GLP-1 Receptor Agonists**:
   GLP-1 receptor agonists such as liraglutide, semaglutide, dulaglutide, and exenatide may be added to metformin therapy in patients requiring additional glycemic control and weight reduction. These agents have also demonstrated cardiovascular benefits in high-risk diabetic populations (Marso et al., 2016).

d) **SGLT2 Inhibitors**:
   SGLT2 inhibitors including empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin are frequently used with metformin because they lower blood glucose through increased urinary glucose excretion and provide cardiovascular and renal protection (Zinman et al., 2015).

e) **Insulin Therapy**:
   In advanced stages of type 2 diabetes, insulin therapy may be combined with metformin to achieve optimal glycemic control. Continuing metformin during insulin treatment often reduces insulin requirements and minimizes weight gain associated with insulin therapy (Nathan et al., 2009).

- **Importance of Metformin in Modern Diabetes Management**:

Despite the emergence of numerous innovative antidiabetic medications, metformin remains the preferred first-line treatment in most international guidelines due to its efficacy, safety, affordability, and extensive clinical evidence (Davies et al., 2018).

Studies conducted by the UK Prospective Diabetes Study Group (1998) demonstrated that metformin not only improves glycemic control but may also reduce diabetes-related complications and mortality among overweight patients with type 2 diabetes.

For these reasons, physician perspectives regarding metformin frequently serve as a benchmark when evaluating newer antidiabetic drugs. Understanding the advantages and limitations of metformin is

therefore essential when comparing it with modern therapeutic agents used in contemporary diabetes management

3. Previous Studies:

Aloufi et al. (2023).
This retrospective study assessed the effectiveness of metformin monotherapy in lowering HbA1c levels i n 136 Saudi Arabian patients with newly diagnosed type 2 diabetes (71 males and 67 females) who had ne ver taken medication before.
The results showed a statistically significant decrease ($p < 0.001$) in the mean HbA1c level from 9.1 to 7. 13 after six months of treatment, indicating that metformin is a successful first-
line treatment choice for newly diagnosed patients of all ages and genders.

In order to give a thorough synthesis of the evidence regarding the efficacy of metformin in preventi ng diabetes and lowering the risk of its progression in at-
risk populations, Patel et al. (2023) carried out a systematic review and meta-analysis.
The final study included 17 studies with a total sample size of 30,474 patients. The researchers colle cted data and published papers up until June 2023 from sources such as PubMed, Scopus, ScienceDi rect, and Google Scholar.According to the meta-
analysis's findings, people with prediabetes who take metformin had a statistically significant 35% l ower chance of developing type 2 diabetes
The results also shown a 42% decrease in risk when compared to non-
metformin control groups, confirming its overall effectiveness in preventing diabetes.
According to the study's findings, metformin is a useful and successful preventative measure to lowe r the total incidence of diabetes, especially in high-risk groups.

Bailey (2024) examined the therapeutic profile of metformin in the treatment and management of type 2 d iabetes. The study noted that metformin has been a first-
line pharmaceutical option to complement patients' lifestyle modifications since its initial clinical usage as a glucose-lowering drug in 1957.
It counteracts insulin resistance and lowers blood glucose without causing weight gain or the danger of ov ert hypoglycemia through a variety of cellular mechanisms, primarily in the gut, liver, and muscle.
The study also mentioned its other advantages, such enhancing lipid metabolism, reducing inflammation, and lowering long-term cardiovascular risks.
The author stressed that metformin can be used in some areas to help with glycemic control during pregna ncy, administered in prediabetes to lower the risk of disease development, and easily coupled with other d iabetic drugs.
The study came to the conclusion that metformin is still a useful therapeutic tool throughout the course of type 2 diabetes because of its well-
established safety profile, affordability, and variety of actions; however, adequate renal function is necess ary to prevent gastrointestinal side effects.

4. Methodology

4.1. Study Objectives:

The current study aimed to achieve the following objectives:

1. To evaluate the effectiveness of Metformin therapy in improving blood sugar levels (fasting and glycated hemoglobin) in a sample of type 2 diabetes patients by comparing measurements before and after the treatment period.
2. To determine the differences in therapeutic response to Metformin between males and females, and to ascertain whether one gender exhibits greater improvement in glycemic control indicators.
3. To explore the relationship between the prescribed Metformin dose (500, 850, 1000 mg) and the degree of improvement in fasting blood sugar and HbA1c levels.
4. To describe the distribution of the study sample according to demographic characteristics (gender, age group) and clinical characteristics (blood sugar level before and after treatment, drug dosage).
5.

4.2. Study Methodology and Procedures:

To achieve the study's objectives, the following methodology and procedures were adopted:

1. **Study Design and Sample:**
   The study employed a retrospective, single-group pretest–posttest (before–after) design based on patients' medical records, without a control group. The study sample consisted of 50 male and female adult patients diagnosed with type 2 diabetes, selected using a purposive (non-probability) sampling method from attendees of an endocrinology and diabetes clinic at el Marj hospital between march and august Inclusion criteria required that the patient be newly diagnosed or treated with metformin only, have no other chronic diseases significantly affecting blood sugar levels, have adhered to the prescribed metformin dose for no less than 3 months, and have complete pre- and post-treatment FBG and HbA1c records. Exclusion criteria were treatment with any other glucose-lowering agent (including insulin), other chronic conditions significantly affecting blood glucose, and incomplete records. Adherence was determined from documented refill.
2. **Description of the Study Sample:**
   The sample included 50 patients, divided equally by gender into 25 males and 25 females. Their ages ranged from 28 to 75 years, and they were classified into six age groups for descriptive and analytical purposes. All participants were receiving metformin therapy at varying doses (500, 850, or 1000 mg) as determined by their treating physician based on their clinical condition; doses were not randomly assigned. Specify formulation (immediate release), dosing frequency, and whether the stated doses are single daily doses.
3. **Data Collection Tools and Variables:**
   Data were collected retrospectively from patients' medical records and included the following variables:
   - **Demographic Variables:** Gender (Male/Female), Age (later converted into age categories).
   - **Independent Variables (Study Factors):** Metformin dose (categorized into three groups: 500, 850, 1000 mg).
   - **Dependent Variables (Treatment Outcomes):**
     Fasting Blood Glucose (FBG) level before and after the treatment period, categorized as: Normal (<100 mg/dL), Pre-diabetes (100-125 mg/dL), and Diabetes (≥126 mg/dL). A "Change in FBG" variable was calculated (post-measurement – pre-measurement) to represent the degree of improvement.
     Glycated Hemoglobin (HbA1c) level before and after the treatment period, categorized as: Normal (<5.7%), Pre-diabetes (5.7-6.4%), and Diabetes (≥6.5%). A "Change In HbA1c" variable was calculated in the same way.

   Follow-up and measurement: Pre-treatment values were those recorded at diagnosis or at the start of metformin therapy, and post-treatment values were those recorded after a follow-up period of at least 3 months (mean follow-up: [_8_ months]). FBG and HbA1c were measured at laboratory The study was approved by ethics committee .

4.3. Statistical Methods Used:

After data collection, data were coded and entered for statistical analysis. The following statistical methods were employed to answer the research questions:

- **Descriptive Statistics:** Frequencies and percentages were calculated to describe the distribution of the sample across categories of demographic and clinical variables (gender, age, blood sugar level, drug dose).

Paired-Samples T-Test: Used to compare mean FBG and HbA1c before and after treatment (with the Wilcoxon signed-rank test as the non-parametric alternative when normality assumptions were not met).

- **Independent Samples T-Test:** Used to compare the mean change (improvement) in FBG and HbA1c levels between the male and female groups.
- **One-Way Analysis of Variance (ANOVA):** Used to compare the mean change (improvement) in FBG and HbA1c levels among the three different Metformin dose groups. Tukey's HSD test was used for post-hoc comparisons to identify the source of significant differences.

- A significance level of $P < 0.05$ (two-tailed) was adopted, and 95% confidence intervals (CI) are reported for mean differences. Data were analyzed using software .SPSS v32; normality and homogeneity of variance were checked using Shapiro–Wilk and Levene's tests.

5. Data Analysis & Results:

5.1. Frequency and Percentage Tables:

Table.1: Distribution of Sample by Gender

Gender	Frequency	Percentage
Males	25	50%
Females	25	50%
Total	50	100%

Table.2: Distribution of Sample by Age Group

Age group	Frequency	Percentage
Less than 30	4	8%
30 – less than 40	8	16%
40 – less than 50	14	28%
50 – less than 60	15	30%
60 – less than 70	7	14%
70 and above	2	4%
Total	50	100%

Table 3: Fasting Blood Glucose (FBG) Category, mg/dL (Before & After Treatment)

FBS Level	Before Treatment		After Treatment	
	Frequency	Percentage	Frequency	Percentage
Normal (<100)	0	0%	22	44%
Pre-Diabetes (100 – 125)	9	18%	21	42%
Diabetes (≥126)	41	82%	7	14%
Total	50	100%	50	100%

Table 4: HbA1c Category, % (Before & After Treatment)

HbA1c Level	Before Treatment		After Treatment	
	Frequency	Percentage	Frequency	Percentage
Normal (<5.7)	0	0%	12	24%
Pre-Diabetes (5.7 – 6.4)	4	8%	27	54%
Diabetes (≥6.5)	46	92%	11	22%
Total	50	100%	50	100%

Table.5: Distribution of Sample by Metformin Dose

Metformin Dose	Frequency	Percentage
500 mg	12	24%
850 mg	18	36%
1000 mg	20	40%
Total	50	100%

5.2. Descriptive Statistics and T- Test for Differences Between Male & Female Means Before & After Treatment:

Table 6: Mean fasting blood glucose (mg/dL) and HbA1c (%) before and after treatment, by gender

Mean change = post-treatment minus pre-treatment value (negative values indicate improvement).

Variable	Gender	N	Mean Before	Mean After	Mean Change
FBS (mg/dL)	Males	25	148.3	112	-36.3
	Females	25	152.1	106.5	-45.6
HbA1c (%)	Males	25	7.9	6.5	-1.4
	Females	25	8.1	6.4	-1.7

Table 7: Independent-samples t-test comparing mean change between males and females

Variable	t-value	Df	P- value	Effect Size (Cohen's d)	Difference in mean reduction, females vs males (95% CI)
Change in FBG (mg/dL)	2.31	48	0.025 (Significant)	0.65 (Medium)	9.3 (1.2 to 17.4)
Change in HbA1c (%)	1.20	48	0.236 (Not Significant)	0.34 (Small)	0.3 (−0.2 to 0.8)

Interpretation of T-Test:

- **Fasting Blood Glucose (FBG):** Females showed a greater mean reduction (45.6 mg/dL) than males (36.3 mg/dL). The difference of 9.3 mg/dL (95% CI 1.2 to 17.4) was statistically significant ($t(48) = 2.31$, $p = 0.025$, Cohen's $d = 0.65$), although the wide confidence interval indicates imprecision in the size of the difference.
- **HbA1c:** Females also showed a numerically greater reduction (1.7% vs 1.4%), but the difference of 0.3 percentage points (95% CI −0.2 to 0.8) was not statistically significant ($p = 0.236$), so the genders can be considered comparable for HbA1c. The two outcomes therefore give inconsistent evidence for a gender effect.

5.3. One-Way Analysis of Variance (ANOVA):

A one-way ANOVA (df = 2, 47) was conducted to compare the mean improvement in FBG and HbA1c according to metformin dose (500, 850, 1000 mg). Table 8 presents the mean change with SD and 95% CI for each dose group.

Table.8: One-Way ANOVA for Drug Dose

Variable	Dose	N	Mean change	SD	95% CI of mean change	F-value (df = 2, 47)	P- value
Change in FBG (mg/dL)	500mg	12	-28.1	15.2	−37.8 to −18.4	6.67	0.003 (Significant)
	850mg	18	-38.9	18.1	−47.9 to −29.9		
	1000mg	20	-50.2	16.5	−57.9 to −42.5		
Change in HbA1c (%)	500mg	12	-0.8	0.5	−1.12 to −0.48	12.82	<0.001 (Significant)
	850mg	18	-1.6	0.7	−1.95 to −1.25		
	1000mg	20	-2.1	0.8	−2.47 to −1.73		

Post-Hoc Tests (Tukey HSD) for Mean Differences:

- **For FBG:** The difference was statistically significant only between the 1000 mg and 500 mg groups (mean difference 22.1 mg/dL, P = 0.002). The differences between 1000 mg and 850 mg (P = 0.107) and between 850 mg and 500 mg (P = 0.207) were not significant.
- **For HbA1c:** The differences were statistically significant between the 1000 mg and 500 mg groups (1.3 percentage points, P < 0.001) and between the 850 mg and 500 mg groups (0.8 percentage points, P = 0.010). The difference between 1000 mg and 850 mg (0.5 percentage points, P = 0.084) was not significant.

Interpretation of ANOVA:

- Metformin dose was significantly associated with the mean reduction in both FBG ($F(2, 47) = 6.67$, $P = 0.003$, $\eta^2 = 0.22$) and HbA1c ($F(2, 47) = 12.82$, $P < 0.001$, $\eta^2 = 0.35$).
- Mean reductions increased progressively with dose (FBG: −28.1, −38.9 and −50.2 mg/dL; HbA1c: −0.8, −1.6 and −2.1%). This should be read as an association rather than a proven dose effect, because doses were assigned by physicians according to clinical need and were not adjusted for baseline glycemia.

6. Discussion

The current study aimed to evaluate the effectiveness of metformin therapy in improving blood sugar levels (fasting and HbA1c) in a sample of patients, in addition to exploring differences in treatment response by gender and drug dose. The results showed an improvement in glycemic indicators after metformin therapy, with variations that warrant careful interpretation.

Firstly, the results are consistent with an improvement in glycemic control after metformin therapy. The frequency tables showed a marked shift in the distribution of patients across blood sugar categories: the percentage classified as diabetic based on FBG decreased from 82% before treatment to 14% after, while the percentage reaching the normal level rose from 0% to 44%. For HbA1c, the proportion in the diabetic range (≥6.5%) decreased from 92% to 22%, while the pre-diabetes and normal categories rose to 54% and 24%, respectively. These findings suggest that, in this sample, metformin was associated with a reclassification of patients from higher-risk to lower-risk glycemic categories, which may help reduce long-term complications, and they are consistent with the literature supporting metformin as a first-line treatment for type 2 diabetes (UK Prospective Diabetes Study Group, 1998; Aloufi et al., 2023). However, without a control group, part of the improvement may reflect regression to the mean, concurrent lifestyle and dietary changes, or the natural course after diagnosis, particularly among newly diagnosed patients.

Secondly, regarding gender differences, both genders improved, but females showed a greater reduction in FBG (45.6 vs 36.3 mg/dL; mean difference 9.3 mg/dL, 95% CI 1.2 to 17.4; P = 0.025; Cohen's d = 0.65), whereas the difference in HbA1c was not statistically significant (P = 0.236). Because HbA1c, the more stable long-term indicator, did not differ significantly, the evidence for a gender effect is limited

and should be interpreted cautiously; it may also be a chance finding given the small sample and the number of comparisons performed. Some studies suggest that women may show higher adherence to therapeutic regimens and medical appointments, and that estrogen may influence insulin sensitivity in pre-menopausal women, but these explanations are hypothetical here, since adherence, menopausal status and baseline glycemia were not adjusted for in the analysis. Confirmation in larger samples is needed before gender-specific follow-up strategies can be recommended.

Thirdly, the one-way ANOVA showed a statistically significant association between metformin dose and the degree of improvement in both FBG and HbA1c. Post hoc tests showed that the 1000 mg group had a larger reduction than the 500 mg group for both indicators, and for HbA1c the 850 mg group also differed from the 500 mg group, whereas 1000 mg versus 850 mg was not significantly different. This pattern is in line with the clinical practice of gradual dose titration, in which treatment starts at a low dose and is increased to reach therapeutic targets (such as an HbA1c below 7%) while monitoring tolerance and side effects. However, doses were prescribed by physicians according to clinical condition rather than randomly allocated; patients with higher baseline glucose, longer disease duration or a poorer initial response may have received higher doses and had more room to improve, so the observed gradient may partly reflect confounding by indication. The absence of a significant difference between the 850 mg and 1000 mg doses suggests that the additional benefit of moving from a medium to a high dose may be modest compared with the greater likelihood of gastrointestinal side effects (Dujic et al., 2016), which supports individualized dosing based on the balance between efficacy and tolerability.

Factors affecting interpretation. Several factors that influence glycemic response were not adjusted for in this analysis, including age (range 28–75 years), baseline FBG and HbA1c, duration of diabetes and of metformin therapy, adherence, diet and physical activity, body weight and renal function. Future studies should use multivariable models (e.g., linear regression or ANCOVA with baseline values as covariates) to estimate the independent effects of gender and dose.

Limitations of the study. The findings should be viewed in light of the following limitations: (1) the relatively small sample (N = 50), selected purposively from a single clinic, which limits generalizability; (2) the single-group pretest–posttest design without a control group, which does not allow improvement to be attributed to metformin alone; (3) the retrospective, record-based data, with possible missing or inaccurate entries and no direct measurement of adherence; (4) unequal dose groups (n = 12, 18 and 20) with doses not randomly assigned; (5) the lack of adjustment for confounders such as age, baseline glycemia and treatment duration; (6) multiple comparisons without correction, so isolated significant results should be treated cautiously; and (7) a follow-up of at least 3 months, which does not capture long-term glycemic control or adverse effects. Accordingly, the results support an association between metformin therapy and improved glycemic indicators but do not permit definitive causal inference.

Conclusion:

In this retrospective single-group study of 50 patients with type 2 diabetes, fasting blood glucose and HbA1c improved after metformin therapy, and most patients moved from the diabetic range to lower-risk glycemic categories. Both males and females improved; females showed a greater reduction in FBG, but the difference in HbA1c was not significant, so the evidence for a gender effect is limited. Higher metformin doses were associated with larger reductions in FBG and HbA1c, the largest being in the 1000 mg group, although this association may be influenced by baseline severity and other unadjusted factors. Given the small sample, the absence of a control group and the retrospective design, these findings support a favorable glycemic response to metformin but do not establish causality. Larger prospective, controlled studies that adjust for age, baseline glycemia, treatment duration and adherence are recommended to confirm the effects of gender and dose and to guide individualized dosing.

7. References

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