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Original article

Effectiveness of Metformin Monotherapy vs. Metformin-Insulin Combination on Glycemic Control for Type 2 Diabetes in Eastern Libya

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Abstract
Type 2 diabetes (T2D) management focuses on achieving optimal glycemic control to mitigate the risk of complications. Metformin monotherapy and metformin-insulin combination therapy are standard treatment approaches. This study aimed to compare the efficacy of metformin monotherapy versus metformin combined with insulin in achieving glycemic control in T2D patients in Eastern Libya. A cross-sectional study was conducted from July 1, 2023, to December 30, 2023, involving 226 participants out of an initial 239, after applying inclusion and exclusion criteria. Eligible participants included T2D patients on metformin monotherapy or combination therapy, aged 18 years and older, with a minimum treatment duration of three months. Exclusion criteria included those on other regimens or newly diagnosed. The final sample consisted of 43.4% males (n=98) and 56.6% females (n=128), with a mean age of 58 years, mean disease duration of 12.9 years, and a mean HbA1c of 7.7%. Of the participants, 91 were on metformin monotherapy, which demonstrated a lower mean HbA1c of 7.1% (±0.93), compared to the 128 participants on metformin-insulin combination therapy, with a mean HbA1c of 8.1% (±1.1). An independent T-test revealed a statistically significant difference ($p<0.001$). These findings suggest that metformin monotherapy may be more effective in achieving glycemic control in certain T2D patients. Future studies are warranted to validate these results and further investigate potential influencing factors.
Keywords: Type 2 Diabetes, Glycemic Control, Metformin Monotherapy, Insulin Combination Therapy, Cross-Sectional Study.

Introduction

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, action, or both. It is classified based on the underlying etiology into type 1 diabetes mellitus (T1D), which is characterized by autoimmune-mediated destruction of pancreatic β-cells responsible for insulin secretion, and type 2 diabetes mellitus (T2D), which arises from peripheral insulin resistance and inadequate insulin secretion to compensate for this resistance [1].

According to the International Diabetes Federation (IDF), approximately 537 million adults aged 20–79 years are living with DM, with over 90% of these cases attributed to T2D. The IDF further estimates that by 2045, the global number of individuals with DM will increase by 46%, reaching 783 million. In contrast to the global average, Libya exhibited a prevalence of 8.7% for DM in 2021, as reported by the World Development Indicators (WDI) [2,3].

Glycemic control refers to the maintenance of glucose concentrations within an optimal range to prevent complications [4]. The American Diabetes Association (ADA) classifies glycemic control based on HbA1c levels into three categories: good (<7%), inadequate (7–8%), and poor (>8%) [5].

A standard measurement for testing and monitoring diabetes mellitus (DM) is the assessment of glycated hemoglobin (HbA1c) levels in the blood, which reflects the average blood glucose concentrations over the past 2 to 3 months [6].

The pharmacological agents used to treat type 2 diabetes (T2D) are collectively referred to as anti-diabetic medications. These include insulin, agents that bind to sulfonylurea receptors to stimulate insulin secretion (e.g., sulfonylureas such as glimepiride), agents that target the liver, muscle, and adipose tissue (e.g., biguanides such as metformin), agents that slow intestinal glucose absorption (e.g., alpha-glucosidase inhibitors), agents that mimic or prolong the incretin effect (e.g., glucagon-like peptide-1 [GLP-1] agonists, dipeptidyl peptidase 4 inhibitors [DPP-4i]), agents that inhibit renal glucose reabsorption (e.g., sodium-glucose co-transporter 2 inhibitors [SGLT2i]), and other agents such as amylin analogs [7].

Metformin is the first-line therapy for T2D and belongs to the biguanide class. It effectively lowers blood glucose with a low risk of hypoglycemia or weight gain. Additionally, metformin acts as an insulin-sparing agent, thereby reducing the daily insulin requirement. Evidence also supports its role in reducing the risk of both macrovascular and microvascular complications [7].

Although metformin is the cornerstone of T2D management, some patients struggle to achieve optimal glycemic control. In such cases, if a patient has been on dual oral anti-diabetic (OAD) therapy for two months with an HbA1c level of 7% or higher, the addition of insulin therapy becomes essential. Insulin enhances glucose uptake in peripheral tissues, thus mitigating insulin resistance and improving glycemic control.

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Furthermore, the combination of metformin and insulin has been associated with a reduced risk of hypoglycemia, weight gain, and both macrovascular and microvascular complications [8,9].
The comparative efficacy of metformin monotherapy versus metformin combined with insulin has been extensively studied. For instance, Paczkowska et al. (2021) compared the effectiveness of metformin monotherapy and a metformin-insulin combination in 140 non-adherent patients with type T2D. The participants were divided into two groups: one received metformin alone, while the other received metformin in combination with insulin. After six months of treatment, both groups exhibited a significant reduction in HbA1c ($p<0.001$), with the combination therapy showing a greater decrease. Similarly, the metformin-insulin combination resulted in a more substantial reduction in fasting blood glucose levels. Additionally, a significant reduction in body mass index (BMI) was observed in both groups, with the combination therapy showing a greater decrease. These findings collectively suggest that the combination of metformin and insulin is more effective in improving key parameters of T2D compared to metformin monotherapy [10]
Additionally, Menesi FA et al. (2017) evaluated the efficacy of three treatment strategies in 100 patients with T2D : metformin monotherapy (Group 1), metformin plus insulin (Group 2), and metformin plus insulin with simvastatin (Group 3). All three regimens led to improvements in fasting blood glucose levels. However, Group 2 demonstrated superior HbA1c reduction compared to Group 1, highlighting the potential benefit of combination therapy [11].
Building upon previous research and addressing the need for further investigation, the present study aims to compare the effectiveness of metformin monotherapy versus metformin-insulin combination therapy in improving HbA1c levels in patients with T2D. We hypothesize that, compared to metformin alone, the combination therapy will result in a greater reduction in HbA1c levels.

Methods

This retrospective cross-sectional study was conducted in eastern Libya at the Benghazi Diabetic Center and Jabal Al-Akhdar Diabetes Center between July 1, 2023, and December 30, 2023.
To ensure a robust comparison of HbA1c levels between metformin monotherapy and metformin-insulin combination therapy, the required sample size was determined using Epi-Info software, yielding 240 participants at a 99.9% confidence level. Participants were selected through simple random sampling, and oral consent was obtained before enrollment. Data collection was carried out using a structured data collection form, which included demoFigureic information, medical history (such as comorbidities), and medication use. HbA1c levels were measured and recorded for each participant.
Of the 320 individuals initially screened, 239 met the inclusion criteria: adults (>18 years) with T2D diagnosed for at least one year and receiving either metformin alone or metformin plus insulin. Among them, 96 participants were assigned to the metformin monotherapy group (Group 1), while 139 were in the combination therapy group (Group 2). Participants were excluded if they were younger than 18 years, newly diagnosed (<1 year), had been on their current regimen for less than three months before data collection, or were receiving treatments other than metformin monotherapy or metformin plus insulin.
Data analysis was performed using SPSS version 25. An independent t-test was used to compare HbA1c levels between the two groups.

Results

General characteristic

Out of 239 participants with T2D, 226 were included in the final analysis. Nine individuals were excluded as outliers, while an additional four were omitted due to missing data. The mean age of the participants was 58 ± 12 years, with an average diabetes duration of 12.9 years. The mean HbA1c level was 7.7 ± 1.2, as presented in Table 1.

Table 1. General characteristics.

Factors	Involved participants
Frequency	226
Mean Age	58 years
Mean diabetic duration	12.9 years
Mean HbA1c (SD)	7.7 (±1.2)

As shown in Table 2, the study included 226 participants, with 91 (40.2%) in the metformin monotherapy group and 135 (59.8%) in the metformin-plus-insulin group. The mean age was 57 years in the monotherapy group and 60 years in the combination therapy group. The average duration of diabetes was 8.6 years in the monotherapy group and 14.5 years in the combination group. Mean HbA1c levels were 7.1 ± 0.9 in the monotherapy group and 8.1 ± 1.1 in the combination therapy group.

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Table 2. Summary Table.

Factors		Metformin Monotherapy	Metformin Plus Insulin Combinations
Frequency		91 (40.2%)	135 (59.8%)
Mean Age		57	60
Mean diabetic duration		8.6 years	14.5 years
Gender	Male (%)	44 (47.8%)	55 (39.9%)
	Female (%)	48 (52.2%)	83 (60.1%)
Mean HbA1c (SD)		7.1 (± 0.9)	8.1 (± 1.1)

Gender distribution of the sample

Figure 1 illustrates the gender distribution of the participants, with 43.36% males and 56.64% females. Additionally, as shown in Table 2, the gender distribution between the two groups was relatively balanced. In the monotherapy group, 47.8% were males and 52.2% were females, while the combination therapy group comprised 39.9% males and 60.1% females.

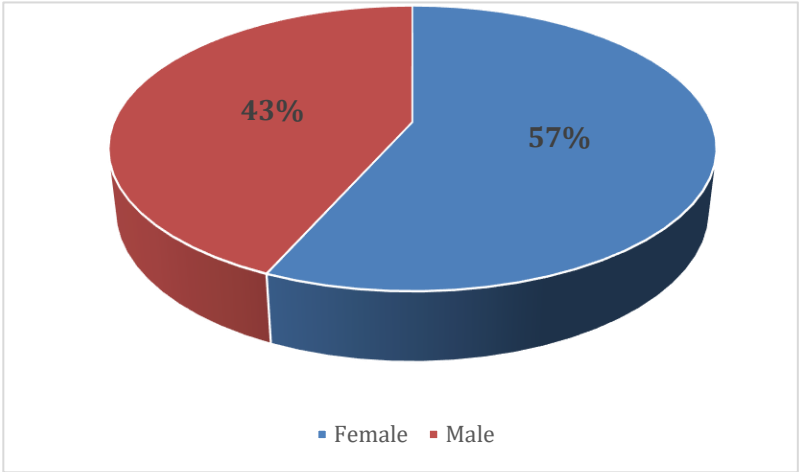

Figure 1. Pie chart of gender distribution of the study sample

Glycemic control of the sample

Figure 2 illustrates the distribution of HbA1c control among all participants, revealing that the majority (76.55%) had either inadequate or poor glycemic control, while only 23.45% achieved good glycemic control.

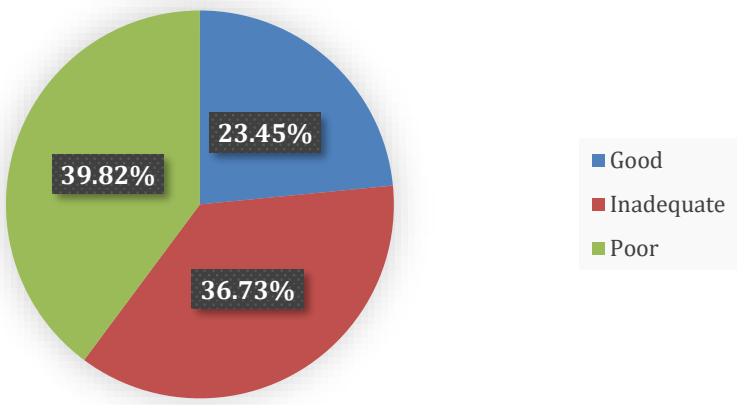

Figure 2. Pie chart showing the glycemic control of the sample.

Table 3 presents the glycemic control levels in patients receiving metformin monotherapy and metformin plus insulin combination therapy. The data indicate that the combination therapy group had a higher percentage of poor glycemic control (53%) compared to the monotherapy group.

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Table 3. Glycemic control between metformin monotherapy versus metformin plus insulin combinations.

Groups	Good	Inadequate	Poor	Total
Metformin Monotherapy	36 (39.56%)	37 (40.65%)	18 (19.75%)	91
Metformin Plus Insulin Combinations	17 (12.59%)	46 (34.07%)	72 (53.33%)	135

Glycemic control between monotherapy group versus combination group

As shown in Table 2, there was a difference in HbA1c levels between the two groups. To determine whether this difference was statistically significant, an independent T-test was performed. Although normality tests were not conducted, visual inspection of the data distribution revealed a symmetrical, bell-shaped curve, suggesting that HbA1c levels were approximately normally distributed. Levene's test for equal variances indicated a statistically significant difference in variances between the two groups ($p = 0.012$). However, given the study's large sample size ($n = 226$), the T-test is considered robust to minor violations of normality. Thus, we focused on the results of Welch's test, which accounts for unequal variances.

As shown in Table 4, the independent T-test revealed a significant difference in HbA1c levels between the metformin monotherapy group (mean = 7.1 ± 0.93) and the metformin plus insulin combination group (mean = 8.1 ± 1.1). The mean HbA1c level in the monotherapy group was 0.99% lower than in the combination therapy group ($t = -7.10$, $p < 0.001$). The 95% confidence interval for the mean difference in HbA1c levels ranged from (-1.27 to -0.72), suggesting that the true difference in HbA1c between the two groups is likely to fall within this range.

While the independent T-test is generally robust to minor violations of assumptions, we also conducted the Mann-Whitney U test to further validate the results. The Mann-Whitney U test, a nonparametric method that does not assume equal variances, yielded results consistent with the T-test ($p < 0.001$). This reinforces the conclusion that there is a statistically significant difference in HbA1c levels between the two groups.

Table 4. Results of Independent T-test for HbA1c Levels.

Hba1c Level	N	Mean	S.D.	T-value	P-value	Mean difference	95% of CI of the difference	
							Lower	Upper
Metformin Monotherapy	91	7.1	± 0.93	-7.1	<0.001	-0.99	-1.27	-0.72
Combination therapy	135	8.1	±1.1					

Discussion

This study investigated the comparative effectiveness of metformin monotherapy versus metformin plus insulin combination therapy in glycemic control. Our findings revealed a statistically significant difference in HbA1c levels, with the monotherapy group exhibiting a lower mean HbA1c compared to the combination therapy group ($p<0.001$). This result was unexpected, as both our initial hypothesis and existing literature generally support the superiority of combination therapy in reducing HbA1c levels. While our study showed lower HbA1c levels in the monotherapy group, prior research has consistently demonstrated that combination therapy achieves greater HbA1c reductions in T2D patients. Studies by Paczkowska et al. (2021) and Menesi FA et al. (2017) both reported superior glycemic control with combination therapy [10,11]. The discrepancy observed in our study warrants further examination. One possible explanation is the difference in sample sizes between the groups. Although the difference in HbA1c was statistically significant, the smaller monotherapy group may have influenced the results. For instance, Paczkowska et al. (2021) conducted a similar study with 140 T2D patients, ensuring balanced group sizes (~70 per group), which yielded findings consistent with the broader literature demonstrating greater HbA1c reduction in the combination therapy group [10,11].

Another potential explanation for the observed difference in HbA1c levels is the variation in baseline glycemic control between the groups. Due to the cross-sectional design of our study, data on HbA1c levels before initiating treatment were unavailable. This limitation may have influenced our findings, as patients in the combination therapy group could have started with higher baseline HbA1c levels and were still in the process of achieving optimal glycemic control. Medication adherence is another critical factor affecting glycemic outcomes. Patients with T2D who do not adhere to prescribed treatments, including oral medications or insulin injections, often experience suboptimal glycemic control. Roaeid et al. (2007) highlighted this issue in a regional study involving 805 patients, where 27.1% reported irregular medication use. Additionally, insulin-specific adherence challenges, such as missed doses and improper injection techniques, were noted.

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Although their study did not specifically assess patients on combination therapy, it underscores adherence difficulties among diabetic patients in the region. In our study, the increased regimen complexity associated with combination therapy may have contributed to lower adherence rates, potentially explaining the higher mean HbA1c levels observed in this group [12].

Our study provides insight into the comparative effectiveness of metformin monotherapy versus combination therapy in T2D management. However, several limitations must be considered. The cross-sectional design captures data at a single time point, preventing causal inference and limiting assessment of baseline HbA1c differences. Longitudinal studies are needed to establish causality. Additionally, the sample size disparity (91 in monotherapy vs. 135 in combination therapy) may have influenced results, necessitating larger, more balanced studies. Moreover, participants were recruited from specific centers (Benghazi Diabetic Center and Jabal Al-Akhdar Diabetes Center), potentially limiting generalizability, as regional variations in treatment practices and demoFigureics could impact glycemic outcomes.

Conclusion

This study evaluated the comparative effectiveness of metformin monotherapy versus combination therapy with insulin in glycemic control among T2D patients. Interestingly, the monotherapy group exhibited a lower mean HbA1c. Although the study has limitations, including sample size and cross-sectional design, the findings highlight the need for further investigation into the potential role of metformin monotherapy in T2D management. Future longitudinal studies with larger, more diverse populations and comprehensive data collection are essential to validate these results and refine treatment strategies.

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Conflicts of Interest

The authors declare no conflicts of interest related to this work.

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المستخلص

يعتمد علاج مرض السكري من النوع الثاني على التحكم في مستويات السكر في الدم لمنع المضاعفات. يعد العلاج الأحادي بالميتفورمين و العلاج المركب الجامع بين الميتفورمين مع الأنسولين من الأساليب العلاجية الشائعة. هدفت هذه الدراسة إلى مقارنة الفاعلية بين العلاج الأحادي بالميتفورمين مقارنةً مع العلاج المركب في تحقيق السيطرة على نسبة السكر في الدم من خلال قياس مستويات الهيموغلوبين السكري. اعتمدت هذه الدراسة تصميمًا مقطعيًا، حيثُ تم تضمين 226 من أصل 239 مشاركًا في التحليل النهائي، تم تجنيدهم من مركز بنغازي لتشخيص و علاج السكري، و مركز الجبل الأخضرللسكري، وعيادة شحات في الفترة من 1 يوليو 2023 إلى 30 ديسمبر 2023. استبعدت الدراسة المشاركين الذين تقل أعمارهم عن 18 عامًا، و المشخصين حديثًا، و أولئك الذين يتبعون نظامًا علاجيًا غير العلاج اللأحادي بالميتوفرمين أو العلاج المركب، والذين تقل مدة استخدامهم للعلاج عن 3 أشهر. تكونت عينة الدراسة النهائية من 43.4% من الذكور و 56.6% من الإناث بمتوسط عمر 58 عامًا، و متوسط مدة الإصابة بالسكري من النوع الثاني 12.9 سنة، و متوسط هيموغلوبين سكري قدره 7.7%. بلغ عدد المشاركين الذين يتلقون العلاج الأحادي 91 مشارك و اظهروا متوسط هيموغلوبين سكري أقل حيث بلغ 7.1% (± 0.93)، مقارنة بالعلاج المركب الذي شمل 128 مشاركًا بمتوسط هيموغلوبين سكري 8.1% (± 1.1). تم إستخدام اختبار (ت) لعينتين مستقلتين، مما أظهر أن الفرق الملاحظ كان ذا دلالة إحصائية. تشير هذه النتائج إلى أن العلاج الأحادي بالميتفورمين قد يوفر تحكمًا أفضل على مستويات السكر في الدم لدى بعض مرضى السكري من النوع الثاني. يُوصى بإجراء المزيد من الدراسات لتأكيد هذه النتائج واستكشاف العوامل المؤثرة.

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