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Assessment of Metformin Failure Among Patients With Type 2 Diabetes Mellitus at a Tertiary Care Center in Central India

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INTRODUCTION

- Type 2 Diabetes mellitus (T2DM) is a non-communicable disease of pandemic proportions.
- India becoming 'diabetes capital of world' with ~ 80 million adult patients.
- Metformin is generally recommended as first-line therapy for T2DM due to high efficacy, low cost and additional benefits.
- Primary or secondary metformin failure is common in clinical practice. and requires appropriate add on 2nd line therapy.
- Patients unable to achieve adequate glycaemic control (HbA1c < 7%) not achieved despite sufficient duration of treatment with maximally tolerated metformin dose (atleast ≥ I g/day)
- Real world evidence (RWE) generation through prospective Comparative Effectiveness Research (CER) study is an important tool to address such issues.

OBJECTIVES

- To characterize metformin monotherapy failure
- To identify factors that predict likelihood of failure to optimise anti-hyperglycaemic therapy.

METHODOLOGY

Study Design: Case Control study
Study Population: T2DM outpatients coming to the diabetes specialty clinics at AIIMS Bhopal, India.
Data collection: From the prescriptions / OPD diaries on the day of clinic visits
Proposed sample size: 60 in each group (Total – 120)

Definitions:

Cases: Those who experienced metformin failure, primary or secondary.
Controls: Those who were adequately controlled on metformin monotherapy.

Inclusion criteria

1. Adult with type 2 diabetes aged 18 years and above of either sex.
2. Patients who gave consent to participate in the study.
3. For cases - Having inadequate glycemic control (HbA1c > 7% and/or FBS > 140 mg/dl) with metformin monotherapy (≥ 1500 mg daily or maximally tolerated dose for ≥ 12 weeks).

For controls - Having adequate glycaemic control control (HbA1c ≤ 7% and/or FBS ≤ 140 mg/dl) with metformin monotherapy

Exclusion criteria

1. Persons with any type of diabetes other than type 2.
2. Having any serious mental illness affecting medication adherence
3. Concomitant administration of strong CYP3A4/5 inhibitors

Statistical Analysis :

- ✓ Data was recorded and analysed using Microsoft Excel version 2021, with calculation of frequencies / proportions, mean / median with standard deviation / interquartile range.
- ✓ Comparisons were done using t test and chi square test.
- ✓ Odds ratio were calculated for factors expected to predict metformin failure.
- ✓ Logistic regression model was generated.

Ethical Considerations:

The study was conducted following the ICH and Indian GCP guidelines.
It was performed after obtaining permission from the Institutional Human Ethics Committee, AIIMS Bhopal (IHEC-LOP/2019/MD0104)

RESULTS

- A total of 124 participants were enrolled - 63 cases and 61 controls.
- Gender distribution showed predominance of males in both groups (59% vs 54%)
- Mean age was also comparable but odds of metformin failure were relatively higher for age < 40 or 50 years.
- Odds of metformin failure were also relatively higher (OR: 1.62) for a BMI ≥ 23 kg/m.
- HbA1c % at therapy initiation was significantly higher in the metformin failure group (8.87 ± 1.63) versus monotherapy controls (7.89 ± 1.45); p = 0.02, OR of 4.33 (1.83-8.26) for HbA1c ≥ 7% and similar difference was seen for FBS (p = 0.03), with an OR of 2.14 for values ≥140 mg/dl.
- The mean blood pressures and lipid parameters were not significantly different in the two groups.
- Medication adherence, pill burden, duration of diabetes, tobacco and alcohol use, family history and history of comorbidities were similar
- In the logistic regression model, duration of diabetes, HbA1c at metformin initiation, and metformin dose at initiation came out to be significant (p≤ 0.05).

Table 1. Demographic and anthropometric characteristics of metformin monotherapy and failure groups

Demographics	Metformin Monotherapy (N =61) n (%) / Mean ± SD	Metformin Failure (N= 63) n (%) / Mean ± SD	p-Value	Mean difference	95% CI of mean difference
Females	25 (41)	29 (46)	0.59	-	-
Males	36 (59)	34 (54)	-	-	-
Age (years)	53.49 ± 12.47	52.05 ± 11.33	0.50	1.44	-2.79-5.68
Age for Females (years)	53.40 ± 11.90	50.72 ± 10.66	0.39	2.68	-3.55-8.90
Age for Males (years)	53.55 ± 13	53.18 ± 11.90	0.90	0.38	-5.58-6.34
Anthropometrics					
Weight (kg)	68.17 ± 12.06	68.76 ± 11.44	0.78	-0.59	-4.77 - 3.59
BMI (kg/m²)	24.95 ± 3.74	25.46 ± 3.75	0.45	-0.51	-1.84 - 0.82
BMI for Females (kg/m²)	25.73 ± 4.20	26.09 ± 4.32	0.75	-0.37	-2.70 - 1.97
BMI for Males (kg/m²)	24.41 ± 3.35	24.91 ± 3.14	0.52	-0.51	-2.06 - 1.04

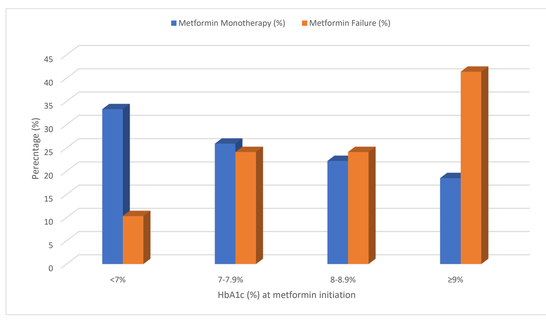

Figure 1. Distribution of HbA1c at metformin initiation

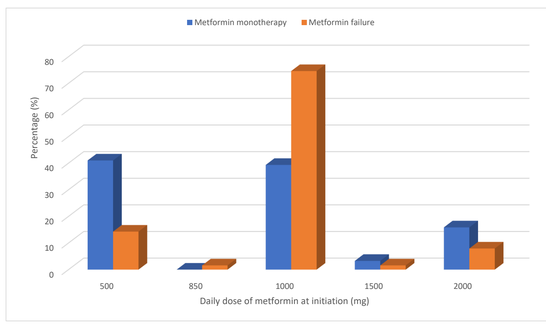

Figure 2. Distribution of Metformin dose at initiation (mg/day)

Table 2. Glycaemic parameters among patients of metformin monotherapy and failure groups

Glycaemic Parameter	Metformin Monotherapy (N =61)	Metformin Failure (N=63)	p-Value	Mean difference	95% CI of mean difference
HbA1c at metformin initiation (%)	7.89 ± 1.45 (n=27)	8.87 ± 1.63 (n=29)	0.02	-0.98	-1.80 – (-0.15)
HbA1c at follow-up (%)	6.76 ± 0.89 (n=41)	8.55 ± 1.42 (n=44)	<0.001	-1.79	-2.30 – (-1.28)
FBS at metformin initiation (mg/dl)	130.22 ± 24.62 (n=25)	153.83 ± 45.15 (n=22)	0.03	-23.61	-45.37 – (-1.86)
FBS at follow-up (mg/dl)	129.75 ± 41.14 (n=37)	168.59 ± 46.40 (n=42)	<0.001	-38.84	-58.60 – (-19.23)
RBS at metformin initiation (mg/dl)	190.33 ± 49.65 (n=15)	221.18 ± 79.40 (n=28)	0.13	-30.85	-70.74 – 9.04
RBS at follow-up (mg/dl)	171.03 ± 64.94 (n=31)	242.99 ± 71.12 (n=41)	<0.001	-71.96	-104.10 - (-39.82)

Log (p/1-p) = -13.72 + 0.187*BMI + 0.679*HbA1c at metformin initiation + 0.002*Duration of Diabetes -0.002* Metformin dose at initiation + Concomitant aspirin + HTN + Hypothyroidism

Conclusion : Our results show that HbA1c / FBS at initiation, age, BMI, dose at initiation could be predictors to identify patients likely to have metformin failure.
Further studies with higher sample size shall validate the results.

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