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Frailty, Medication Adherence, and Glycemic Control in Patients with Type 2 Diabetes: A Cross-Sectional Study Among Metformin- and Non-Metformin-Exposed Groups

ABSTRACT

Objective: Type 2 diabetes (T2D) is a non-communicable disease that contributes to frailty. Metformin is a widely used medication for managing blood sugar, and it may help reduce frailty. This study aimed to investigate the relationships between frailty, medication adherence, and glycemic control in metformin-exposed (ME) and non-metformin-exposed (NME) patients with T2D.

Materials and methods: This prospective cross-sectional study was conducted to assess frailty and medication adherence in patients with T2D divided into ME and NME groups using Fried's Frailty Assessment and the medication adherence questionnaire, respectively. Data were summarized using descriptive statistics, and Spearman's Rank Correlation Coefficient was used to associate frailty and medication adherence.

Results: A total of 126 patients with T2D were enrolled. More of the ME group (16 persons [19.0%]) were non-frail than in the NME group (2 [4.8%]). More of the ME group (18 [21.4%]) had high adherence compared to the NME group (8 [19.0%]). More of the patients in the ME group (11 [13.1%]) had HbA1c < 6.5% than in the NME group (4 [9.5%]). There was no significant correlation between medication adherence and frailty, neither in overall patients (p = 0.313) nor between the groups of ME (p = 0.547) and NME (p = 0.442). A significant correlation between frailty scores and glycemic control was observed in the overall patients (p = 0.045), but significance was not found within the ME (p = 0.236) and NME groups 0.062.

Conclusions: There is correlation between frailty and glycemic control among patients with T2D. Metformin treatment was linked to a lower frailty risk, underscoring the need for personalized diabetes management.

The study has been registered under Clinical Trial Registry of India with the registration number CTRI/2023/11/059585. https://ctri.nic.in/Clinicaltrials/login.php?id=

Keywords: frailty, HbA1c, medication adherence, metformin

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Introduction

Type 2 diabetes (T2D) is a metabolic disorder, characterized by abnormally elevated blood glucose levels that can be detected using random blood glucose, fasting blood glucose, or two-hour plasma glucose. After China, India is the second most prevalent country worldwide for diabetes. The International Diabetic Federation (IDF) estimated that 537 million individuals between the ages of 20 and 79 years were diabetic globally in 2021, and it is predicted that by 2030 there will be 643 million individuals worldwide with diabetes. In Bangladesh, Nepal, India, and other Southeast Asian nations, there are 90 million individuals who have diabetes. In 2011, the World Health Organization recommended that, where feasible, countries and regions should consider using glycated hemoglobin (HbA1c) levels of ≥6.5% as a diagnostic threshold for diabetes [1–3].

One of the significant complications of T2D is frailty. Frailty is a condition characterized by diminished functional reserve and susceptibility. It is a significant public health concern because of its association with systemic disorders, elevated risk of hospitalization, and death. Normally, it is often associated with aging and poor health outcomes; however, in patients with T2D, the prevalence of frailty syndrome is 32-48% and is an independent risk factor. Diabetes has a complicated physiology that requires several treatments for effective control of disease. Biguanides like metformin are the most commonly used oral antidiabetic medication. The two major targets of metformin are insulin resistance and chronic inflammation, which are also the two prevalent causes of T2D and frailty [4–6].

Along with the medication, the prevention of T2D requires long-term adherence to medication interventions with proven lifestyle changes, which prevents complications like frailty. Poor adherence to the treatment results in the advancement of illness symptoms and these consequences have been associated with non-adherence such as frailty. Adhering to anti-diabetic medications enhances glycemic regulation, thereby diminishing the likelihood of complications and fostering a more favorable prognosis; it also has an economical advantage by curbing hospitalization rates and associated expenditures. Numerous obstacles contribute to non-adherence, including the presence of multiple comorbidities and polypharmacy among patients with diabetes [7–9]. There have been very few studies conducted in India on frailty and medication adherence. So, this study aimed to investigate the relationships between frailty, medication adherence, and glycemic control in metformin-exposed and non-exposed patients with diabetes.

Materials and methods

Study design

A cross-sectional study was carried out to assess the frailty, medication adherence, and glycemic control among 126 T2D patients. The study was carried out in the Department of General Medicine and Department of Endocrinology in a Charitable Hospital over a period of six months (October 2023 — March 2024).

Study population/Study participants

T2D patients aged 19 to 59 years were enrolled and divided into two groups, i.e., a metformin-exposed (ME) group and a non-metformin-exposed (NME) group. Patients who had been using metformin for at least two years, either alone or in conjunction with other anti-diabetic medications, including insulin, were included in the ME group. The NME group comprised patients who had been on other anti-diabetic drugs, including insulin, but had not taken metformin for a minimum of two years. Patients with dementia, Parkinson's disease, severe depression, neurological disorders, or those unable to complete the study procedures were excluded. Breastfeeding and pregnant women, as well as patients diagnosed with type 1 T2D, were excluded from the study.

Ethical approval

The study was approved by the NGSM Institute of Pharmaceutical Sciences-Institutional Ethics Committee (NGSMIPS-IEC) [NGSMIPS/IEC/]0018/2023] and was registered under Clinical Trial Registry-India (CTRI) [CTRI/2023/11/059585]. Participants were provided with an approved patient information sheet, clarified their queries, and were recruited after the investigator obtained their informed written consent. The study procedure was carried out as per the guidelines laid down in Declaration of Helsinki 1964 and revised later.

Data collection

Data were collected using a patient data collection form, which was designed according to the study's requirement. All the relevant details pertaining to the study were collected. The socio-demographic details including age, gender, weight, height, body mass index (BMI), educational status, occupation, and socioeconomic status were assessed using the modified Kuppuswamy socioeconomic status scale [10]. Information regarding the number of anti-diabetic drugs and comorbid conditions and lab values like HbA1c were collected. According to ICMR guidelines, glycemic control was measured using HbA1c levels, with a target of below 6.5% in both groups [11].

Frailty assessment

Frailty was assessed using Fried's Frailty Phenotype scale, based on the five characteristics weight loss, exhaustion, weakness, low physical activity, and slowness. The scale categorized patients as frail (≥ 3), pre-frail (1–2), and non-frail (0). A dynamometer was used to measure the participants' grip strength, and this measurement was essential for determining their level of weakness [12].

Medication adherence assessment

Medication adherence was assessed through a medication adherence questionnaire (MAQ) with eight self-reported questions with yes or no answers to evaluate medication adherence. These responses were converted to a 0 to 100 score. Based on the scores, the MAQ divided the patients into three adherence categories: a score of 100 indicated high adherence, a score between 75 and less than 100 signified medium adherences, and a score below 75 indicated low adherence [13].

Statistical analysis

The study used convenience sampling method to calculate the sample size using the comparison of two proportions (unequal allocations, i.e., 2:1). The expected proportion in the ME group was 0.131, and the expected proportion in the NME group was 0.36 [14]. The estimated difference was found to be –0.229. At a 5% level of significance and 80% power, the required sample size was 126, with 84 patients in the ME group and 42 in the NME group. The sample size was calculated using n-master software version 2.0.

Mean ± standard deviation (SD), frequency (%), and median were used to summarize the descriptive data of the study. Pearson's chi-square test was used to compare baseline characteristics between the metformin-exposed and non-metformin-exposed groups. Spearman's rank correlation coefficient was used to examine the association between frailty and glycemic control as well as between frailty and medication adherence. SPSS version 29.0 was used for the analysis.

Results

Among the total 126 enrolled patients, the majority were males (70 [55.6%]). Of these, 43 (51.2%) belonged to the ME group and 27 (64.3%) to the NME group. There were no patients in either group under the age of 30 years. The majority of patients were between the ages of 50 and 59 years in both the ME (61 [72.6%]) and NME groups (29 [69.0%]). BMI was assessed and categorized. Most of the patients had normal BMI in both the ME group (57 [67.9%]) and the NME group (19 [42.5%]). The modified Kuppuswamy socioeconomic scale was used to determine socioeconomic class. Most patients belonged to the lower middle class in both the ME (29 [34.5%]) and the NME group (14 [33.3%]). The social habits of the enrolled patients were collected. Most patients in both the ME group (48 [57.1%]) and the NME group (25 [59.5%]), had no social habits. This was followed by alcohol consumption in both groups, with 16 (19.0%) in the ME group and 9 (21.4%) in the NME group, respectively. To ensure balanced enrollment, a chi-square test was conducted in sociodemographic characteristics to assess differences between the two groups. A non-significant p-value ($p > 0.05$) was observed in all demographic characteristics, indicating no statistically significant differences between the groups, and this suggests that the groups were comparable.

The numbers of anti-diabetic drugs prescribed were collected. The majority of the patients in the ME group (50 [59.5%]) were prescribed two anti-diabetic drugs. In the NME group (32 [76.2%]) the majority of the patients were prescribed with anti-diabetic monotherapy. Comorbidity was assessed. Hypertension was found to be the major comorbidity in both the ME (42 [50%]) and NME group (29 [69%]) followed by dyslipidemia in both the groups. HbA1c was collected to evaluate the level of glucose control. Most of the patients in both the ME group (73 [86.9%]) and the NME group (38 [90.5%]) were found to have high HbA1c levels (Tab. 1).

Frailty assessment

Frailty status was assessed using Fried's Frailty Phenotype Criteria. In the whole group of patients, the majority (56 [44.4%]) were found to be pre-frail. Most of the patients in the ME group (40 [47.6%]) were found to be pre-frail whereas the majority of the patients in the NME group (24 [57.1%]) were found to be frail. There was significant difference between the ME group and the NME group, with participants in NME group more likely to be frail than participants in the ME group, with a p-value of 0.015. Frailty was assessed by gender. In the ME group, most males (24 [28.5%]), were categorized as prefrail, followed by females (16 [19.0%]) in the prefrail category. In the NME group, the majority of females (13 [30.9%]) were categorized as prefrail, followed by males (12 [28.5%]), and females (12 [28.5%]) in the frail category (Tab. 2).

Among all patients, a significant correlation was observed between frailty score and extent of glycemic control, indicating that patients with an HbA1c level of 6.5% or higher are more inclined to be frail ($p = 0.045$). Insignificant correlation ($p = 0.236$ for the ME group and $p = 0.062$ for the NME group) was

Table 1. Sociodemographic and Clinical Parameters

Characteristics	Metformin exposed (ME), n = 84 (%)	Non-metformin exposed (NME), n = 42 (%)	P-value
Gender			
Male	43 (51.2)	27 (64.3)	0.163
Female	41 (48.8)	15 (35.7)	
Age [years] wise distribution			
Mean age ± SD	52.1 ± 5.9	51.1 ± 6.2	0.754
BMI [kg/m^2] categorization			
Mean BMI ± SD	23.5 ± 3.4	24.3 ± 5.3	0.015
Socioeconomic status			
Upper class (I)	12 (14.3)	11 (26.2)	0.359
Upper middle class (II)	24 (28.6)	11 (26.2)	
Lower middle class (III)	29 (34.5)	14 (33.3)	
Upper lower class (IV)	19 (22.6)	6 (14.3)	
Social habits			
Smoking	6 (7.14)	2 (4.76)	—
Alcohol	16 (19.04)	9 (21.4)	
Tobacco chewing	6 (7.14)	3 (7.14)	
Smoking + alcohol	5 (5.95)	2 (4.76)	
Smoking + tobacco	—	1 (2.38)	
Alcohol + tobacco	2 (2.38)	—	
Smoking + alcohol + to-	1 (1.19)	—	
bacco	48 (57.1)	25 (59.5)	
No habits			
No. of Anti-diabetic drugs			
1	17 (20.2)	32 (76.2)	—
2	50 (59.5)	8 (19.0)	
3	15 (17.9)	2 (4.8)	
4	2 (2.4)	—	
HbA1c [%]			
< 6.5%	11 (13.1)	4 (9.5)	0.958
≥ 6.5%	73 (86.90	38 (90.5)	
Mean HbA1c ± SD	8.3 ± 1.6	8.6 ± 1.7	0.365
Comorbidities			
Hypertension	42 (50)	29 (69)	—
Hypothyroidism	7 (8.3)	3 (7.1)	
Dyslipidemia	8 (9.5)	7 (16.7)	
Anemia	2 (2.4)	7 (16.7)	
CVA	5 (6)	6 (14.3)	
Others*	5 (5.9)	6 (14.2)	

Others* (ME group): asthma, COPD, liver disease; Others* (NME group): liver disease, COPD

BMI — body mass index; CVA — cerebrovascular accident; HbA1c — glycated hemoglobin; SD — standard deviation

observed between frailty and HbA1c levels among the ME and NME groups (Tab. 3 and 4).

Medication adherence assessment

Medication adherence was assessed and categorized using MAQ. Most of the patients in the ME group were in the low adherence category (44 [52.4%]) followed by medium adherence (22 [26.2%]). Most of the patients in the NME group showed medium adherence (20 [47.6%]) followed by low adherence (14 [33.3%]). There was a statistically significant difference observed between the ME group and the NME group, with a p-value of 0.046. Correlation between frailty and medication adherence was observed. Among all enrolled patients, there was no significant correlation between frailty and medication adherence, with a p-value of 0.313. Additionally, within the ME group and NME group, no significant correlations were found, with

Table 2. Frailty, Medication adherence and HbA1c levels between metformin exposed and non-metformin exposed groups

Frailty	Metformin exposed n = 84 (%)	Non-Metformin exposed n = 42 (%)	P-value
Non-frail	16 (19.0)	2 (4.8)	
Pre-frail	40 (47.6)	16 (38.1)	0.015**
Frail	28 (33.3)	24 (57.1)	
Medication Adherence			
High adherence	18 (21.4)	8 (19.0)	
Medium adherence	22 (26.2)	20 (47.6)	0.046**
Low adherence	44 (52.4)	14 (33.3)	
Mean ± SD	82.1 ± 22.02	81.8 ± 22.5	
HbA1c [%]			
< 6.5%	11 (13.1)	4 (9.5)	0.958
≥ 6.5%	73 (86.9)	38 (90.5)	
Mean ± SD	8.3 ± 1.6	8.6 ± 1.7	

**significant at < 0.05; HbA1c — glycated hemoglobin; SD — standard deviation

Table 3. Correlation of Frailty with HbA1c Levels and Frailty with Medication Adherence

Variable	Median (IQR)	Correlation coefficient (ρ)	P-value
Frailty	2 (1, 3)	0.179	0.045**
Median (Q1, Q3)			
HbA1c	8.15 (7.1, 9.8)		
Median (Q1, Q3)			
Variable			
Frailty	2 (1, 3)	–0.091	0.313
Median (Q1, Q3)			
MAQ	87.50 (75, 100)		
Median (Q1, Q3)			

*Spearman's Rank correlation coefficient; **significant at < 0.05; HbA1c — glycated hemoglobin; IQR — interquartile range; MAQ — medication adherence questionnaire

Table 4. Correlation between Frailty with HbA1c in the ME and NME Groups and Frailty and Medication Adherence in the ME and NME Groups

Groups	Variable	Correlation coefficient (ρ)	P-value
Metformin exposed	Frailty	0.131	0.236
	HbA1c		
Non-metformin exposed	Frailty	0.291	0.062
	HbA1c		
Groups	Variable	Correlation coefficient (ρ)	P-value
Metformin exposed	Frailty	–0.067	0.547
	Medication adherence		
Non-metformin exposed	Frailty	–0.122	0.442
	Medication Adherence		

HbA1c — glycated hemoglobin; ME — metformin-exposed; NME — non-metformin-exposed

p-values of 0.547 for the ME group and 0.442 for the NME group regarding frailty and medication adherence among patients with diabetes (Tab. 2–4).

Discussion

Diabetes presents multifaceted challenges, including frailty, affecting patient prognosis. Medication

adherence is crucial for managing diabetes effectively. Metformin, a key treatment, may impact frailty and adherence. However, research on these interactions is lacking [15, 16].

Among all the enrolled patients, most were males, which is in line with the study by Tang et al. [17], in which the majority of the enrolled patients were males. In the study setting, males were predominant in both the ME and the NME group, which was similar to the study by Liu et al. [14]. This is because middle aged males are more likely to have T2D compared to females [18].

Socioeconomic assessment was done based on the modified Kuppuswamy socioeconomic status scale and categorized based on the scores. In the present study, 43 (34.1%) patients belonged to lower middle class (III), which was similar to the study conducted by Prasad et al. [19], in which 38.88% of patients were in upper lower class.

In the current study, 58 (46%) patients were treated with dual therapy, while the remaining 49 (38.9) received anti-diabetic monotherapy, which was slightly different compared to the study by Agarwal et al. [20], in which most of the patients were treated with monotherapy (59%).

In the present study settings, it was found that 57.1% of individuals in the NME and 33.3% of participants in the ME group were frail. Frailty for the ME group and the NME group showed clinical significance ($p = 0.015$). Therefore, using metformin has been found to be independently linked to a lower risk of frailty in patients with diabetes. This was comparable with the research carried out by Bhaskaran et al. [21], Liu et al. [14], and Sumantri et al. [22]. Patients belonging to the NME group were found to be more frail compared to the ME group; this may be because metformin delays frailty by enhancing insulin sensitivity, reducing inflammation, and displaying geroprotective properties [5, 23].

Of all the patients enrolled in this study, 26 (20.6%) were found to be highly adherent to their medication, 42 (33.3%) showed medium adherence, and 58 (46%) showed low adherence. This was found to be similar to a study carried out by Sahoo et al. [9], wherein 34.14% of patients were found to be adherent to their medication. A study conducted by Syafhan et al. [24] showed that the majority of the T2D patients (61.2%) were not adherent to the medication, which is in agreement with the current study. This may be because many patients had concerns regarding the safety of the medication and the economical aspect, which impacted adherence. This issue can be addressed by educating the patients about the disease and their medication, and by educating the patients about the generic substitutions of branded drugs which are more cost-effective [3, 24].

Our study also revealed that the groups exposed to metformin had higher medication adherence compared to the non-metformin group. This was comparable to a study conducted by Lee et al. [25]. Their research revealed that metformin users consistently exhibited the highest rates of adherence and persistence. In the present study, in comparison to the NME groups (14 [33.3%]), low adherence was more common in the ME groups (44 [52.4%]), which is comparable to the study by McGovern et al. [26] in which patients on metformin were shown to have lower adherence than non-metformin users. The majority of our patients in the ME groups were on dual therapy (50 [59.5%]); similarly, a lot of patients in the ME groups were on dual, triple, and quadruple therapy compared to the NME groups. An increased number of medications could have been one of the reasons for decreased adherence in the ME groups.

Our study revealed no correlation between medication adherence and frailty ($p = 0.313$). The studies carried out by Wang et al. [27] and Qiao et al. [28] demonstrated that frailty greatly influenced medication adherence, which was in conflict with our study. However, both of these studies were conducted on a group of elderly people.

In the current study, there were more patients who had HbA1c levels $\geq 6.5\%$ in the ME group. There was no statistical significance found ($p = 0.958$). This was in opposition to research conducted by Nishimura et al. [29], which found that metformin improved glucose control. Our research indicates that there is an association ($p = 0.045$) between glycemic control and frailty, indicating that glycemic deficiencies in glucose control are a substantial risk factor for frailty. This was comparable to the study by Kulkarni et al. [30]. On the other hand, observations made by Yanagita et al. [31] yielded contradictory results, although this study was conducted in the Japanese elderly population.

One of the major limitations of our study was the small sample size and short duration of study. Our study helps fill existing knowledge gaps and offers a clearer understanding of how metformin influences frailty in a younger population. Research on the relationship between frailty and metformin use is limited, with studies suggesting it lowers frailty risk in older patients with diabetes. However, understanding metformin's effects on frailty, medication adherence, and glycemic control in adults aged 19–59 years is lacking. Examining this in a younger population may yield useful information.

Conclusions

In conclusion, our research reflects on the complex associations between medication adherence, frailty, and glycemic control in patients with diabetes, particularly when metformin treatment is involved. There was a noteworthy decrease in risk of frailty in patients exposed to metformin (16 [19.0%]). Furthermore, patients from the metformin-exposed group (18 [21.4]) showed higher adherence than the non-metformin exposed group (8 [19.0]). In our study, frailty and medication adherence did not show correlation; however, there was a significant association between frailty and glycemic control. Overall, further research is required into this topic to draw precise conclusions and interpretations.

Article information

Data availability

The authors declare that data related to the study will be made available upon request.

Author contribution

LKC, LVM, ESP: design, literature search, data acquisition, manuscript preparations; SShetty: data analysis and statistical analysis; UVM, AK, SSirimalla: conceptualization, manuscript editing, manuscript review; UVM: guarantor.

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Conflict of interest

The authors declare no conflict of interest.

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