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MEDICATION REGIMEN COMPLEXITY ASSESSMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS IMPACT ON MEDICATION ADHERENCE AND GLYCEMIC CONTROL: A CROSS-SECTIONAL STUDY IN TERTIARY CARE HOSPITAL, SOUTH KERALA

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ABSTRACT: Background and Aim: The prevalence of DM worldwide is estimated to be 415 million, which is anticipated to surpass 642 million in the next 25 years. Good glycaemic control reduces the incidence of complications associated with diabetes and thus improves microvascular diseases. Complexity can be regarded as the root cause of low adherence and thus result in interactions. This study aimed to evaluate the complexity of medication regimens in patients diagnosed with diabetes mellitus and its impact on medication adherence and glycaemic control. **Methodology:** A hospital-based cross-sectional study was conducted on 265 patients with diabetes in NIMS Medicity, Kerala, for 6 months, and the association between predictive and outcome variables was analyzed. **Results:** The final analysis included 265 diabetic patients who met the inclusion criteria. Around 66.03% of patients showed a high level of patient-specific MRCI, while 3% had high diabetes-specific MRCI. Almost 26.4% of patients showed high compliance with diabetic medications. Most patients included in the study (66%) showed poor glycemic control. The patients with severe patient-specific MRCI showed more non-adherence (p<0.001), while in the case of diabetic-specific MRCI, patients with low and moderate levels had high non-adherence. Also, those patients with diabetes duration greater than 10 years and those with co-morbidities showed more non-adherence, which was statistically significant. Patients with severe patient-specific MRCI (p<0.001) and increased age of above 61 years had poor glycemic control. There was no remarkable association of drug interaction with both diabetic as well as patient-specific MRCI.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disease characterized by elevated glucose levels. Diabetes is a complex, heterogeneous metabolic disorder characterized by elevated blood glucose levels due to either resistance insulin effect, inadequate insulin secretion, or both [2].

Low- and middle-income countries comprise the world's majority of diabetic cases, which encompasses India after China [3, 5]. Diabetes is the primary cause of morbidity and mortality in the US, with an expenditure of about 760 billion dollars, accounting for 10% of total adult expenses [6, 7]. Obesity has a strong association with diabetes. Increased BMI and elevated waist-hip ratio augments the diabetic risk.

Along with diabetes, the terrifying conditions are its co-morbidities, which stretch out from microvascular to macrovascular complications. There remains a linear relationship between the

duration of diabetes and the development of diabetic complications [3]. Around 25–40% of diabetic patients develop microvascular complications with a mean age of over 25 years with more than 5 years of diabetes [8]. Patients with type 1 diabetes mellitus (T1DM) are associated with a higher risk of coronary artery disease (CAD) [9]. Some researchers suggested from their observation that both microvascular and macrovascular complications progress simultaneously in diabetic patients over 5 years or more [10].

Poor glycemic control leads to a burden in terms of health resources and medical care costs. American Diabetic Association recommends <7% of HbA1C as the target range [11,] focusing on reducing cardiovascular risk. The incidence of poor medication adherence in the diabetic population ranges from 38-93% [12, 13]. The reduced adherence includes poor medication adherence to complex oral and injectables, psychological insulin resistance, weight gain following insulin injection, and concerns about the tolerability of insulin [14, 15]. An increased hike of about 40% of the occurrence of a cardiovascular event in HbA1C elevated patients [16].

The major adverse cardiac events are observed in patients with HbA1C≥6.5% [17]. Evidence concludes that patients who underwent coronary angiography with higher HbA1C were a predictor of disease severity associated with coronary artery disease. Oral hypoglycemic agents and injectables (insulin) are the preferred therapy for diabetes. The therapy adherence and the diabetic population are also recommended to take follow-ups every six months. They should get their treatment modified according to the laboratory result from the physician.

Some patients do not even have any record of laboratory tests done, which accounted for a non-adherence rate of about 35%. Patients with multiple chronic diseases were more adherent than those with single chronic disease conditions [18]. There is a 0.16% reduction in HbA1C with a 10% increase in medication adherence. Improving medication adherence and educating patients regarding the importance of medication adherence, along with follow-up and prescription refills, must be considered. Poor medication adherence results in

treatment failure in 30-50% of cases. Medication regimen complexity is the count of prescribed medications in simple terms. But it also considers the dosage form, frequencies, and usage direction. Patients receiving treatment with high regimen complexity are linked to poor adherence [19], leading to poor clinical outcomes. Medication adherence of a patient depends on many factors, out of which the major one is medication regimen complexity [20].

Polypharmacy is defined as five or more prescription drugs associated with worse outcomes. Most medication intakes were mainly related to treating co-morbidities [21], suggesting that comorbid conditions increase the risk of inappropriate medication use. There is a decrease in medication adherence even with the change from once-daily to twice-daily dosing [22]. More medications with special instructions lead to poor interest and high patient difficulty. Complexity can be regarded as the root cause of poor adherence. In our study, we assessed the role of medication regimen complexity and medication adherence and also the occurrence of interaction in the outcome of patients. Such a study using MRCI and diabetes complications has not yet been carried out in Kerala. Therefore, the present study aimed at correlating adherence and medication regimen complexity among individuals with type 2 diabetes mellitus in a tertiary care hospital.

METHODOLOGY:

Study Design, Study Area, Study Period and Sampling Technique: A hospital-based cross-sectional study was carried out on 265 diabetes patients in NIMS MEDICITY, a tertiary care hospital in Thiruvananthapuram, India. The study lasted 6 months from April 2021 to September 2021. A Convenience sampling technique was used in the study.

Inclusion and Exclusion Criteria: All inpatients and outpatients above 18 years with a duration of diabetes above 5 years were included in the study. The excluded group includes critically ill patients who cannot participate in interviews. Patients with gestational diabetes were also excluded from the study.

Sample size Determination: The formula for determining sample size is:-

$$n = Z^2 p\,(1-p) / d^2$$

Where n is the sample size, Z indicates the level of confidence, P shows expected prevalence or proportion and d is the Precision. Therefore,

$$n = (1.96)^2\,0.222\,(1-0.222) / (0.05)^2$$

$$= 265 \text{ patients}$$

Data Collection Procedure and Methods: Clinical data, socio-demographic data, and patients' current medication details were obtained from the patient chart. The patients were asked about their medication adherence using a pre-validated questionnaire, and the answers were recorded simultaneously.

Data that were unavailable from the patient chart, like the medication history, medication adherence data, and other missing demographic details, were also obtained by direct interviews with the patients

Medication Regimen Complexity Index (MRCI): A validated 65-item tool used mainly for quantifying drug regimen complexity based on the number of medications, dosage form, dosage frequency, and additional instructions like break/crush the tablet, take with specific fluid, *etc*.

The Malaysia Medication Adherence Assessment Tool (MyMAAT): Medication adherence was measured using 'The Malaysia Medication Adherence Assessment Tool' (MyMAAT). This validated 12-item tool facilitates the correct interventions by identifying patients' potential reasons for medication non-adherence.

Data Entry and Statistical Analysis: The data were analyzed using IBM SPSS Statistics for Windows, V.26.0. Statistics including variable frequencies, mean (age, duration of diabetes, glycaemic control) and percentage were calculated to do the analysis.

Association between predictive variables (regimen-related complexity, sociodemographic details, and clinical data of patients) was done using binary logistic regression. Univariate logistic regression was used to analyze the association between an individual independent variable and the outcome of interest. It was tested to calculate the odds ratio (OR). Statistical significance was determined at p value<0.05.

Ethical Consideration: Written informed consent, necessary permission, and clearance for the study were obtained from the Institutional Ethical Committee of NIMS Medicity, Trivandrum and approved with an IEC approval number NIMS/IEC/2021/03/04.

RESULT:
Socio-demographics and Clinical Characteristics: A total of 265 cases of diabetes mellitus were analyzed, of which higher proportion were males, with a greater age group from 45 to 60 years. About half of the sample population had diabetes for 5-10 years.

TABLE 1: SOCIO-DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Gender	N(%)
Male	156(58.9)
Female	109(41.1)
Age (years)	
18-60	112(42.19)
>60	153(57.81)
Education	
Illiterate	10(3.8)
Primaryschool	38(14.3)
Middleschool	102(38.5)
Highschool	66(24.9)
Diploma	27(10.2)
Graduate	17(6.4)
Postgraduate	5(1.9)
Income	
<2640	29(10.9)
2641-52733	236(89.1)
Duration Of Diabetes (in years)	
≤10	127(47.9)
>10	138(52.1)
Co-morbidity	
Present	233(87.9)
Absent	32(12.03)
HbA1C	
<7	90(34)
≥7	175(66)
Complications	
Microvascular	136(51.33)
Macrovascular	129(48.67)

The presence of comorbid condition was studied and it was found that about 87.9% of the population

were having hypertension, dyslipidemia, chronic liver diseases, *etc*. 25.7% were having an HbA1C range from 6-7. CAD was concluded to be the most occurring complication of DM which is about 24.5%.

The least occurring diabetic complication was found to be stroke (1.5%). Details of other characteristics are given in **Table 1.**

Medication Regimen Complexity, Adherence and Glycemic Control: Patient-related MRCI had a cut-off value of 11.25. A higher ratio shown severe patient-level MRCI. High patient population falls under the moderate category diabetes related MRCI (63.2%).

While comparing both diabetes-related and patient-related MRCI, patient-related MRCI was found to be more than diabetic-related MRCI **Table 2**.

Around 70 patients (26.4%) were found to be more adherent to the medications. 66% of the whole population were having poor gycemic control whereas 34% were found to have good glycemic control.

TABLE 2: MEDICATION REGIMEN COMPLEXITY, ADHERENCE, GLYCEMIC CONTROL

Item	%
Diabetic-related regimen complexity	
Low	33.8
Moderate	63.2
High	3
Patient-related regimen complexity	
Low	1.9
Moderate	32.07
High	66.03
Medication adherence	
Adherent	26.4
Non- adherent	73.6
Glycaemic control	
Good	66
Poor	34

Association of Medication Regimen Complexity and Other Variables with Level of Adherence: Most patients with severe MRCI had poor adherence according to MyMAAT scores. Patients with diabetes duration for more than 10 years had poor medication adherence, which was statistically significant (p <0.001**). In diabetic-specific MRCI, most of the non-adherent patients had moderate MRCI scores. Other associations are listed in **Table 3.**

TABLE 3: ASSOCIATION OF MEDICATION REGIMEN COMPLEXITY AND OTHER VARIABLES WITH LEVEL OF ADHERENCE

Variables	Adherence Level		Odds Ratio (Ci-95%)		
MRCI	Adherent	Non-Adherent	Or	Ci	p-value
Patient-specific					
MRCI Low	3	2	4.4659	0.7225-27.6051	0.1073
MRCI	23	62	8.0257	4.4582-14.4478	<0.001*
Moderate MRCI	44	131	1	1	-
Severe MRCI					
Diabetes specific					
MRCI, Low	27	63	0.7143	0.1593-3.2035	0.6603
MRCI	40	127	0.5249	0.1201-2.2941	0.3917
Moderate MRCI	3	5	1	1	-
Severe MRCI					
Sex					
Male	41	115	1	0.5648 to 1.7125	0.9531
Female	29	80	0.9835		
Age					
18-25	-	-	-		
26-44	5	26	-	1	-
45-60	18	63	1	0.2686 to 11.1870	-
61-75	27	68	1.733	0.2166 to 6.2842	0.5632
76-90	18	32	1.1667	0.1594 to 4.4209	0.8576
91 &above	2	6	0.8395	0.1081 to 3.2482	0.8365
			0.5926		0.5466
Education					
Illiterate	3	7	1	0.2293 to 4.8263	0.9480
Primary school	11	27	1.0519	0.3016 to 5.2033	0.7564
Middle school	26	76	1.2527	0.2662 to 4.9063	0.8574

High school	18	48	1.1429	0.2086 to 4.9656	0.9825
Diploma	8	19	1.0179	0.2405 to 8.0675	0.7116
Graduate	4	13	1.3929	-	-
Postgraduate	0	5	-		
Income	11	18	1		
<2640	20	53	1.6194	0.6522 to 4.0213	0.2989
2641-7886	15	45	1.8333	0.7084 to 4.7445	0.2115
7887-13160	14	51	2.2262	0.8565 to 5.7862	0.1006
13161-19758	7	19	1.6587	0.5272 to 5.2184	0.3868
19759-26354	3	9	1.8333	0.4064 to 8.2714	0.4304
26355-52733	0	0	-	-	-
>52733					
Duration (in	57	70	7.8297	4.0077 to 15.2967	<0.001*
years) ≤10 >10	13	125			
Co-morbidity					
Present	55	178			
Absent	15	17	2.8556	1.3391 to 6.0897	0.0066*

Association of Medication Regimen Complexity and Other Variables with Glycemic Control: The relationship between patient-related MRCI and glycemic control showed that there is a profound association when comparing moderate to severe MRCI with glycemic control. A significant association was noted while comparing age and glycemic control. Diabetes duration of greater than 10 years showed poor glycemic control with a statistically significant association of p < 0.001**. The Association of MRCI and other variables with glycemic control is enlisted in **Table 4.**

TABLE 4: ASSOCIATION OF MRCI AND OTHER VARIABLES WITH GLYCEMIC CONTROL

Variable	Glycemic Control		Odds Ratio		
MRCI	POOR(>7)	GOOD(≤7)	OR	CI	p-VALUE
Patient specific MRCI					
Low MRCI	5	0	1	-	-
Moderate MRCI	15	76	0.9749	0.0513 to 18.52	0.9865
Severe MRCI	155	14	5.609	2.5756 to 12.2169	<0.001*
Diabetes specific					
MRCI	6	2	1		
Low MRCI	40	12	0.5658	0.1114 to 2.8740	0.4922
Moderate MRCI	129	76	0.5092	0.2517 to 1.0302	0.0605
Severe MRCI					
Sex					
Male	73	36	1		
Female	102	54	0.9315	0.5550 to 1.5634	0.7883
Age					
18-25	-	-	-		
26-44	16	15	1	-	-
45-60	63	18	0.3125	0.0544 to 1.7956	0.1923
61-75	74	21	0.0952	0.0177 to 0.5130	0.0062*
76-90	20	30	0.0946	0.0178 to 0.5036	0.0057*
91 & above	2	6	0.5000	0.0916 to 2.7299	0.4235
Education					
Illiterate	8	2			
Primary school	29	9	1.2414		
Middle school	78	24	1.2308		
High school	44	22	2.0000	-	-
Diploma	9	18	8.0000		
Graduate	3	14	18.666		
Post graduate	4	1	-		
Income					
<2640	10	2	1		
2641-7886	25	15	3.0000	0.5777 to 15.5842	0.1913
7887-13160	60	31	2.5833	0.5327 to 12.5281	0.2387

13161-19758	45	28	3.1111	0.6345 to 15.2534	0.1617
19759-26354	21	7	1.6667	0.2918 to 9.5204	0.5656
26355-52733	10	6	3.0000	0.4838 to 18.6021	0.2380
>52733	4	1	1.2500	0.0869 to 17.9759	0.8697
Duration (in years)					
≤10	103	24	-	-	-
>10	72	66	0.2542	0.1458 to 0.4431	<0.001*
Co-morbidity					
Present	155	78			
Absent	20	12	1.1923	0.5545 to 2.5640	0.6525

Association of MRCI with Drug Interaction: Study reveals an increase in MRCI is not a contributing factor to the incidence of drug interaction **Table 5**. In the association between patient-related MRCI and drug interaction, most cases with severe MRCI had moderate drug interactions. Most patients with a severe diabetic-specific MRCI had moderate drug interactions.

TABLE 5: ASSOCIATIONOFMRCIWITH DRUG INTERACTION

Drug interaction	PATIENT-SPECIFIC MRCI			ODDS RATIO		
	Low	Moderate	Severe	OR	CI	p-value
No interaction	1	1	16	2.4187	0.6661 to 8.7833	0.1795
Minor	1	17	35			
Moderate	3	35	82			
Major	0	3	17			
	Diabetic-Specific MRCI			0.7174	0.2355 to 2.1854	0.5589
No interaction	1	3	14			
Minor	2	13	38			
Moderate	5	22	92			
Major	0	5	15			

DISCUSSION: The study used a pre-validated instrument to measure the medication regimen complexity and assess the impact on patients' medication-taking behavior. 156 men and 109 women with diabetes who participated in the research provided samples, whereas males were the majority in another study [23]. Most of the participants who responded were between the ages of 61 and 75, accounting for 35.84% of the total sample. 38.5 percent of participants had completed middle school, compared to 24.9 percent who had finished high school, and most had low incomes. The findings were in contrast to those of the study[23]. The presence of comorbid disorders was analyzed, and a more significant percentage of 87.9% was reported, identical to another study on the co-morbidity burden of type 2 diabetes mellitus [24].

The gold standard for determining glycemic control is HbA1C. The RBS and HbAIC tests were used assess glycemic control and were the critical parameters we used to assess glycemic control in diabetic patients. The American Diabetes Association recommends a goal range of 7% HbA1C for good glycemic management. The majority of the population, around 66%, had poor glycemic control, meaning their HbA1C was above 7%. The research found that a cardiovascular complication, which affected 24.5 percent of the patients, was the most frequent diabetic complication, followed by CKD at 9.4% and foot ulcer at 7.2%. This was consistent with the findings of another two studies that found foot ulcer the most frequent diabetic complication [25, 26]. The results of this study show that diabetic patients frequently experience minor drug interactions. People with diabetes who take many medicines run the risk of drug interactions.

Patients with low and moderate MRCI are more adherent, according to study [23]. Patients using many medications reportedly had a more difficult medication regimen, leading to poor adherence and worse patient outcomes, according to another research [20]. Patient education is the most crucial step in preventing incorrect beliefs about anti-diabetic treatment, which can result in poor drug consumption and non-adherence. A variety of circumstances influence adherence to diabetic medication. We discovered a strong association between moderate patient-related MRCI and

medication adherence. As demonstrated in a study, the duration of diabetes of more than 10 years and the presence of co-morbidity were significantly associated with adherence level [23].

The study showed a similar finding, suggesting that a greater diabetes-specific MRCI results in reduced glycemic management [27]. Glycemic control was favorably linked with age in our study. Glycemic control was inadequate in patients aged 61 to 90 years (p < 0.0062). Glycemic control and diabetes duration were found to be having a substantial relationship. Patients with diabetes for more than ten years have poor glycemic control. According to the study, Glycemic control was thought to be hampered by pharmaceutical factors like regimen complexity and drug adherence [23]. MRCI was found to be severe. However, the study found a significant frequency of diabetes-specific MRCI in similar research [23]. The high complexity of diabetic patients' prescription regimens is common and may contribute to non-adherence. Patients who did not properly take their diabetes medicine as prescribed had low glycemic control, which resulted in poor clinical outcomes.

CONCLUSION: Our study concludes that increased medication regimen complexity in patients with diabetes is a major risk factor for non-adherence. Patient-level MRCI was comparatively higher than diabetic-level MRCI. The complexity associated with a pharmaceutical regimen can raise the danger of drug interactions. Non-adherence was higher among patients with low and moderate diabetic-specific MRCI. Patients with severe diabetic-specific MRCI showed poor glycemic control, which is lower in elderly diabetic patients due to co-morbidities, social and economic level, physical and mental status, and perception of the condition. CAD was the most common complication among diabetes patients. As per our findings, the majority of patients had co-morbidities, which had a significant impact on adherence. Due to the increased drug complexity and burden, patients may choose to skip the medication. Thus streamlining the drug regimen can lower the incidence of medication complexity and the social and financial load on patients. Switching to long-acting pharmaceuticals requiring fewer doses per day, employing combination products, and consolidating routes of administration are all ways to reduce medication complexity. Giving patient's advice regarding the importance of medication adherence and glycemic control could help them have a better clinical outcome.

CONFLICTS OF INTEREST: Nil

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