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Factors affecting the level of medication adherence to anti-diabetic treatment: A multi-center cross-sectional study in Eastern Bhutan

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ABSTRACT

Background: Worldwide, Diabetes Mellitus affects millions of people. It is a chronic and progressive disease requiring a long-term treatment plan, adherence to which becomes extremely challenging. Globally, there is a poor level of medication adherence to anti-diabetic treatment and several studies have explored the factors affecting medication adherence. However, in Bhutan, there is limited data on the rate of medication adherence and factors affecting it. . Therefore, the study aimed to find the level of anti-diabetic medication adherence and factors affecting it. **Methods:** A multicenter cross-sectional observational study was conducted involving six eastern district hospitals from June 2019 to February 2020. Research participants were randomly selected from the daily cohort of patients visiting diabetic clinics. **Results:** Amongst the 390 participants, the overall level of adherence reported in this study was intermediate with a mean Morisky Medication Adherence Scale 8 Items (MMAS-8) score of 6.06 (95% CI 5.91-6.22). Nearly 40% demonstrated a low level of adherence (MMAS-8 score <6). There was a statistically significant ($p<0.05$) association between mean MMAS-8 scores and adverse drug reactions, the drug regimen (polypharmacy or monotherapy) and the type of diabetes mellitus. **Conclusion:** This study revealed an intermediate level of medication adherence to anti-diabetic treatment in the eastern region of Bhutan. Adverse drug reactions and polypharmacy resulted in a lower level of adherence. However, further studies are needed to draw a definitive conclusion.

Keywords: *Adherence level; Bhutan; Diabetes Mellitus; Morisky; Risk factors.*

INTRODUCTION

Diabetes Mellitus (DM) is a chronic and progressive disease with a global prevalence of 10.5% (536.60 million people) in 2021[1]. Over the past few decades, the number of diabetic patients has risen faster in low and middle-income countries. Bhutan reported an incidence of 75-82 persons per 10,000 people in 2020[2].

Non adherence to medication is a major concern for all chronic diseases requiring life-long treatment[3]. Medication adherence is the extent to which a patient gets treatment in accordance with the prescribed interval and dose[4]. Though it is a global concern, medication adherence is generally considered poor worldwide, with minimal importance accorded to it even during hospital consultations[5,6].

Although Bhutan shares concerns on the low level of medication adherence to chronic diseases and its related consequences, there are no studies examining the level of medication adherence. With this lack of data, health consequences due to nonadherence to prescribed treatment could be significant. In order to address this knowledge gap, this study intended to study the level of adherence and risk factors affecting anti-diabetic treatment in eastern region of Bhutan.

METHODS

The study was a multicenter cross-sectional observational study conducted in six district hospitals in eastern Bhutan. It was conducted from June 2019 to February 2020.

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Study population and sampling technique

Diabetic patients (both DM type 1 and 2) above the age of 18 years visiting the diabetic clinics of the 6 eastern hospitals were eligible participants. Those with gestational DM and mentally challenged patients without a capacity to consent were excluded from the study. A simple randomization technique was used for recruiting participants, wherein every third or fifth diabetic patient visiting the diabetic clinic who fulfilled the inclusion criteria were approached for inclusion into the study. They were enrolled after receiving informed written consent.

The sample size was calculated based on an estimated total number of patients with DM in Bhutan of 15,000 in the year 2019 and a non-adherence rate of 50% to the treatment. A minimum sample size of 375 was calculated, considering a 95% confidence interval with a margin of error of 5%. To offset loss of subjects through refusal to consent or incomplete data, we took a sample size of 400.

Data collection

Data was collected by focal persons of DM clinic working in the six identified hospitals. Some of these hospitals operate diabetic clinics daily whereas others operate two to three days a week. Each recruited participant was provided with information about the research and consent for participation was obtained. The diabetic clinic's focal person collected relevant data by reading out questions from a structured questionnaire.

The questionnaire consisted of socio demographic details, details about the type of DM, type of treatment regimen (mono or polytherapy), route of administration of medications, history of any adverse drug reactions, presence of any other co-morbidity, and the time taken to reach the nearest health facility. The Morisky Medication Adherence Scale 8 Items (MMAS-8) was also a part of the questionnaire, to determine the level of adherence. The MMAS-8 is a tool which has been tested and validated in many languages for chronic diseases requiring long term treatment[7-9].The owner of the tool granted us the permission to use the tool via certificate Number: 1207-2004-207-3141-8477.

MMAS-8 consists of 8 closed-ended questions. Except for item number 8, all other questions are responded with either Yes or No. Each 'Yes' response is accorded a score of '0' while each 'No' response is accorded a score of 1, except for item 5, where 'Yes' response is scored 1 and 'No' response is scored 0. Item number 8 includes a 5-point Likert response (0-4), corresponding to scores of 0, 0.25, 0.50, 0.75, and 1, respectively As per the MMAS-8 score, the level of medication adherence can be high (=8), intermediate (6 & 7) or low (< 6)[7].

Statistical analysis

For descriptive analysis of continuous variables, mean and SD were employed and for categorical variables, percentages were used. For inferential analysis, Chi-square test was used. Statistical analysis was conducted using EpiData Software Version 3.1. The primary outcome of this study was to find the level of adherence to anti-diabetic medications, and were reported as being low, intermediate or high.

Ethical clearance

For this study, ethical approval was accorded by the Research Ethics Board for Health, Ministry of Health, Bhutan (Ref. No. REBH/Approval/2019/022 23/06/ 2019 dated 23/06/ 2019).

RESULTS

Of the 400 participants recruited, 390 were included in the analysis. To analyse the primary outcome of level of medication adherence, only 383 were included since 7 had missing data. Figure 1 depicts the process of patient recruitment and analysis.

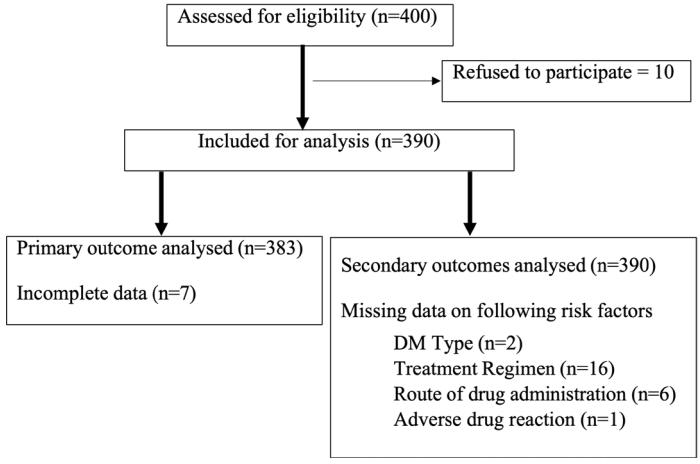

Figure 1. Flow diagram depicting the process of recruitment of participants in the six eastern district hospitals of Bhutan, June 2019-February 2020

The majority of the participants in this study (49.20%) were availing services from the Eastern Regional Referral Hospital (ERRH). Females outnumbered males (54.4% vs. 45.6%) and participants in the age group of 51-65 years constituted the majority (161, 41.3%). As depicted in Table 1, patients with Type 2 DM (378, 97.4%) outnumbered those with Type 1 DM and a majority of them (257, 65.90%) had an additional co-morbidity. Most of the participants (361, 94%) were on oral hypoglycemic agents and most did not report experiencing an adverse effect to treatment (314, 80.70%).

The overall mean MMAS-8 score was 6.06 (95% CI 5.91-6.22). Amongst the 383 participants included in the analysis of the primary outcome, 16.40% (n=63) reported high level of adherence, 41.30% (n=158) reported intermediate level of adherence and 42.30% (n=162) reported a low level of adherence.

Table 1. Baseline characteristics of participants in the six eastern hospitals of Bhutan, June 2019-February 2020, n=390

Variables	N (%)
Sex	
Male	178 (45.6)
Female	212 (54.4)
Age group	
<35 years old	13 (3.30)
35-50 years old	122 (31.30)
51-65 years old	161 (41.30)
>65 years old	94 (24.10)
Education level	
Illiterate	287 (73.60)
Literate	103 (26.40)
Occupation	
Employed	86 (22.10)
Retired	29 (7.40)
Farmer	177 (45.40)
Housewife	98 (25.10)
Type of DM	
DM Type 1	10 (2.60)
DM Type 2	378 (96.90)
Missing data	2 (0.50)
Co-morbidity	
Yes	257 (65.90)
No	133 (34.10)
Treatment Regimen	
Monotherapy	185 (47.40)
Polytherapy	189 (48.50)
Missing data	16 (4.10)
Route of administration	
Oral	361 (92.60)
Injection	7 (1.80)
Both oral and injection	16 (4.10)
Missing data	6 (1.50)
Adverse drug reaction	
Yes	75 (19.20)
No	314 (80.50)
Missing data	1 (0.30)
Hospitals	
Eastern Regional Referral Hospital	192 (49.20)
Trashigang District Hospital	62 (15.90)
Pemagatshel District Hospital	48 (12.30)
Samdrup Jongkhar District Hospital	50 (12.80)
Lhuentse District Hospital	50 (12.80)
Lhuentse District Hospital	16 (4.10)
Trashi Yangtse District Hospital	22 (5.60)
Average time taken to reach health facility	
<1 hour	191 (49.00)
1-3 hours	179 (45.90)
>3 hours	20 (5.10)

Patients availing DM treatment at Samdrup Jongkhar district hospital reported the lowest mean MMAS-8 score of 4.46 while patients availing DM treatment at Trashi Yangtse district hospital reported the highest mean MMAS-8 scores of 6.73. The mean scores of patients from other hospitals ranged from 5.73 to 6.63 as reflected in Figure 2.

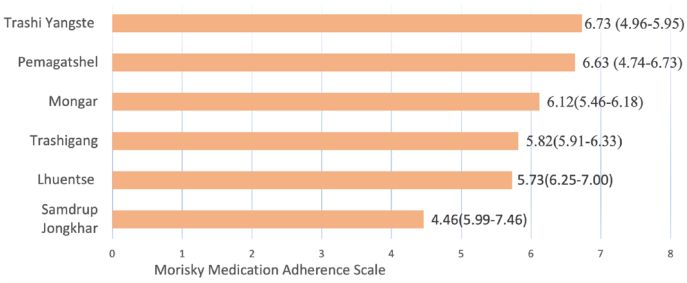

Figure 2. Bar graph depicting mean MMAS-8 score in 6 hospitals of Bhutan. [The numbers at the end of bar represent means scores with 95% confidence intervals within brackets.]

Adverse reactions to anti-diabetic drugs, types of treatment regimen (polypharmacy or monotherapy) and the type of DM demonstrated a statistically significant ($p<0.05$) association with mean MMAS-8 score, as shown in Table 2.

Table 2. Risk factors affecting the medication adherence amongst diabetic patients availing services at six eastern hospitals of Bhutan, June 2019-February 2020, n=390

Risk factors	Adherence scores		p-value
	Mean score	95% CI	
Age group			
<30 years	6.25	5.36 – 7.14	0.46
35 – 50 years	5.93	5.66 – 6.19	
51 – 65 years	6.04	5.78 – 6.30	
>65 years	6.26	5.96 – 6.55	
Sex			
Male	6.01	5.78 – 6.24	0.58
Female	6.10	5.88 – 6.31	
Marital status			
Married	6.05	5.89 – 6.21	0.59
Unmarried	6.21	5.61 – 6.82	
Level of education			
Literate	6.08	5.90 – 6.26	0.82
Illiterate	6.04	5.72 – 6.36	
Occupation			
Employed	5.97	5.63 – 6.31	0.21
Retired	6.22	5.52 – 6.93	
Farmer	5.92	5.70 – 6.14	
Housewife	6.22	6.00 – 6.63	
Treatment regimen			
Monotherapy	6.28	6.06 – 6.49	0.00
Polytherapy	5.84	5.62 – 6.06	
Types of diabetes mellitus			
Continued...			
Type 1	4.95	3.84 – 6.06	0.02
Type 2	6.09	5.94 – 6.25	
Route of drug administration			
Oral	6.08	5.92 – 6.24	0.14
Injection	4.93	2.83 – 7.03	
Both	6.02	5.28 – 6/75	
Presence of co-morbidities			
Yes	6.17	5.98 – 6.35	0.06
No	5.86	5.58 – 6.14	
Average travel time to nearest health facility			
<1 hour	6.13	5.90 – 6.36	
1 – 3 hours	6.00	5.78 – 6.22	0.74
>3 hours	6.05	5.27 – 6.83	
Are you informed on the need to take medicines / injection if you don't feel any symptoms?			
Yes	6.02	5.86 – 6.18	0.05 (One-way ANNOVA)
No	6.35	5.81 – 6.89	
Do you know why you are taking medications?			
Yes	6.10	5.95 – 6.26	0.10
No	5.64	5.04 – 6.24	

DISCUSSION

With an overall mean MMAS-8 score of 6.06, this study reports an intermediate level of adherence to oral anti-diabetic drugs amongst diabetic patients availing services from six hospitals in the eastern part of Bhutan. However, 42% of participants reported a low level of medication adherence, which is concerning. This rate is similar to the global adherence rate of below 50%[6,10,11]. Even developed countries like the USA have reported that 40% of patients with Type 2 DM are nonadherent, the United Kingdom reports that 39.9% were nonadherent, and China reports a non-adherence rate of 54.6% amongst diabetic patients[7,12,13]. However, our neighboring country India has reported a lower non-adherence rate of 25.5% amongst diabetic patients availing services from 3 government hospitals in Delhi[8].The studies in the United Kingdom and China only assessed adherence to oral diabetic agents and excluded those using insulin.

Low level of medication adherence amongst diabetic patients is associated with poor glycemic control, diabetic micro and macro vascular complications, and eventual increased morbidity and mortality[12]. In the long run, it not only affects physical health of the patients but also becomes a financial burden to a country[9,13].

While comparing mean MMAS-8 scores among diabetic patients availing services from the 6 eastern hospitals, the current study noted that participants from Samdrup Jongkhar district

reported the lowest level of adherence whereas participants from Trashi Yangtse district revealed the highest level of adherence. Samdrup Jongkhar has only 7 primary health care centers, 3 sub-post facilities and 1 district hospital to cater to its population of 35,079. Except for one additional sub-post, the number of healthcare facilities have remained the same since 2018[14,15]. This could be a potential reason why they had the lowest adherence. However, disproportionate sampling from the various hospitals could have impacted the mean adherence rates. A study in rural Kerala in India reported poor adherence in 74% of diabetic patients using the MMAS-8 tool[16]. Rural areas usually have poor socio-economic conditions which may influence the adherence level.

Higher levels of education have been reported to bring about a positive influence on medication adherence[10,12]. However, findings of our study did not reveal a significant association of level of education with medication adherence levels. This may be because health advocacy programs are regularly conducted in local languages by health assistants in the primary health care centers in Bhutan. Thus, the level of formal schooling may have limited influence on the understanding of being adherent to medications.

This study, however, demonstrated a significant association between mean MMAS-8 score and polypharmacy. A similar finding was also revealed in other studies where multiple drug regimens were associated with reduced levels of medication adherence[9,10]. The need to take multiple drugs make the treatment complex with a potential for forgetting a few doses[16,17]. An adverse event with the medication has been reported to adversely affect medication adherence[18]. This study noted a statistically significant association between a past episode of adverse drug reaction and the level of medication adherence.

The strength of this study is that it was conducted in a free healthcare setting involving 6 district hospitals of eastern Bhutan, which represents 24% of Bhutanese population[19]. However, the authors also admit to have few limitations. The study experienced a few dropouts due to incomplete data and the sample size was not proportionate among the districts.

CONCLUSION

An intermediate level of adherence to oral and injectable anti-diabetic medicine is noted amongst diabetic patients in the eastern region of Bhutan. While it is premature to draw any conclusion with just one study, this sets the stage to conduct other studies to address factors resulting in nonadherence to medications.

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AUTHORS CONTRIBUTION

TW: Concept, design, data collection and analysis, manuscript writing &review
PN: Concept, design, data collection and analysis, manuscript writing & review
SD: Concept, design, data collection & review
ST: Concept, design, data collection & review
DW: Concept, design, data collection & review
KW: Concept, design, data collection & review
TW: Concept, design, data collection & review
TN: Concept, design, data collection & review
Authors agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST
None
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