Medication Adherence in Patients with Type 2 Diabetes in India- Issue and Solution

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Abstract
Adherence to diabetes medication is one of the most important determinants for the effectiveness of therapy because poor adherence can hinder optimum clinical benefit. Adherence to treatment not only achieves a desirable glycaemic level, but on a longer run reduces the morbidity and mortality among patients with diabetes. Thus, it is imperative to identify the root cause of nonadherence to medication among diabetes patients. It is erroneous to presume that nonadherence is due to patient-related factors arising out of his/her own behaviour or indifference toward the disease. In fact, studies across India have identified forgetfulness and side effects as contributors to poor adherence to diabetes medication. Extended-release formulations and diabetes smart apps can be considered as good tools to assist people in adhering to their medications.
Keywords: Type 2 diabetes mellitus, adherence, extended-release formulations, immediate release formulations, apps

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I. Introduction

Diabetes is the ninth leading cause of death globally and has acquired the status of being the largest global public health emergencies of the century. The scenario is grimmer for the low- and middle-income countries like India where diabetes has reached epidemic proportions [1]. According to the International Diabetes Federation (IDF), 2019, India is home to 70 million individuals with diabetes and the number is estimated to increase to (101.0 and 134.2 million) by 2030 and 2045 respectively [2]. Diabetes being a progressive disease, if inadequately controlled, could lead to serious macrovascular and microvascular complications as well as the recently recognized non-traditional complications such as mental health, cancer, disability, and liver disease [1,3]. Death is the most feared outcome of diabetes-related complications, and India has already suffered 1 million deaths so far [1,2]. According to the India State-Level Disease Burden Initiative Diabetes study, death rates due to diabetes in India are on an increasing trend, with a reported 131% increase from 1990 to 2016 [4].

To curb the epidemic of diabetes and its associated complications, we need to study factors contributing to good glycaemic control (HbA1c <7%). One of the major factors that contributes to adequate glycemic control in patients with type 2 diabetes mellitus (T2DM) is good treatment adherence [5,6]. An inverse relationship has been established between diabetes medication adherence and hemoglobin A1c [7].

Adherence according to WHO, is defined as "the extent to which a patient's behaviour of taking medication, is in line with that recommended by his physician" [8]. Nonadherence to treatment could occur at different stages of the treatment and has been a major hurdle in the management of diabetes by healthcare providers [9]. Besides being associated with unfavourable outcomes like uncontrolled blood sugar and diabetes related complications, non-adherence to taking medication in diabetic patients increases, mortality, the use of health services, treatment costs and the country's economic burden [10-12]. Further nonadherence would lead to straining the healthcare system, an impact that would be more evident in the low- and middle-income countries like India, that is also among the top three countries with a largest number of adults with diabetes [13].

The problem of non-adherence is high and universal, in both developed and developing countries [12]. This article aims to discuss the incidence of adherence and determinants of non-adherence among diabetes patients in India and the effectiveness of tools that are being developed to assist in adherence.

II.   Non-adherence to medication- Prevalence in India

Six independent studies have estimated the prevalence of non-adherence to diabetes medication in the south of India. A hospital-based cross-sectional study by Olickal*et al*, in Puducherry, from March 2019 to February 2020, on 1002 patients, found the prevalence of poor adherence to be 39.5% (95% CI 36.5–42.6%), using the Morisky, Green, and Levine Adherence scale (MGL) in Tamil [14].Pritika*et al* found the overall prevalence of non-compliance to be 29.7% (95% CI 24.5-34.8%) in a community based cross–sectional study in rural and urban Chennai, on 300 patients with type 2 diabetes [15]. Padmanabha*et al* in a study in rural and urban Bengaluru on 250 patients with type 2 diabetes, found 62% to be adherent and 38% to be non-adherent to anti diabetic medications, using the 8 item Morisky's treatment adherence scale [16]. Medi *et al* concluded the overall medication adherence rate to be 47.85%, in a cross-sectional observation study in 140 patients, in a super speciality hospital in Manipal Karnataka. Adherence in this study was assessed using a structured medication adherence questionnaire. Additionally, the study found that 28.57% patients missed daily dose sometimes (less than 5 doses per week), whereas 23.57% of patients frequently missed daily doses (more than 5 doses per week) [17]. Thapar *et al*, in their study at Kasturba Medical College, Mangalore, found 43.5% of the 124 participants to have low adherence to anti-diabetes medication, using the Morisky 8-Item Medication Adherence Questionnaire [13]. The lowest rate of medication adherence i.e. 15% was observed by Rani *et al* in a study on 200 diabetic patients in three public health hospitals in South India [18].

Three studies to estimate compliance were conducted in the north of India. The first study was in a tertiary teaching centre in New Delhi wherein, medication adherence, as estimated with a 4-item Morisky scale, was good (Morisky score ≥3) in only 47.7% of patients[19].Misra*et al* reported 39.4% adherence to the treatment of diabetes mellitus in the rural community of north India, Ballabgarh. The study was conducted on 400 patients and drug adherence was determined by both recall and pill count method.20 Bansal *et al* observed compliance to medication in 82.5% patients from rural area of Ludhiana district, India [21].

Compliance was evaluated in two independent studies in the west of India. Kotian*et al* in a community-based, cross-sectional, study in three urban slums of Belapur, Navi Mumbai observed that 96.5% patients with diabetes missed the medication. Compliance in this study was measured by recall method and recording the number of missed doses over 2 weeks prior to the date of interview [22]. Chavan *et al* reported pharmacological compliance by 76.2% amongst 307 participants, in cross-sectional study conducted in a rural health centre attached to a medical college from Sangli district of Maharashtra [23].

A six-month observational study by Roy et al reported 44.62%, overall prevalence of therapeutic non-adherence (score >2 with MMAS-8 scale) in 257 patients, at KPC Medical College and Hospital, Kolkata [24].

III.   Factors associated with Nonadherence to Antidiabetic medication

3.1 Forgetfulness

Several studies conducted in different parts of India, have cited forgetfulness as the most common reason among study participants for not taking their diabetes medication regularly [13,16-18,22,24].

Thapar *et al* have reported forgetfulness as a reason for not taking medication in 40% of study participants [13]. Kotian*et al,* observed difficulty to remember to take daily medication due to work or forgetfulness in 49.41% of patients with diabetes [22]. Medi *et al* also noted forgetfulness (n = 36, 46.75%) and being busy (n = 34, 44.15%), as the main factors for non-adherence [17]. Rani T *et al*, in their study revealed that 56% of the patients mentioned that they forgot to take medicines when away from home and/or traveling and 67% said they just forget to take medicines [18]. Rani S *et al* have cited forgetting to take medications as the foremost reason for poor adherence, with a mean score of 3.12 on the Morisky's eight-item treatment adherence scale [16]. Roy *et al*, too in their study indicated forgetfulness as the topmost reasons for non-adherence to medication and observed it in 57.59% of the study population [24].

3.2   Factors contributing to Forgetfulness

3.2.1 Frequent dosing

A clear inverse relationship between compliance and the number of daily doses has been demonstrated in several studies [25-29]. In the area of diabetic care too, it was found that regimen complexity including more frequent dosing was related to poorer adherence to oral hypoglycaemic medication [30-31].

Dezii*et al.* compared adherence in once-daily dosing and twice-daily dosing of glipizide in patients with type 2 diabetes and found a higher compliance in the once-daily dosing group (60.5%) than the twice-daily dosing group (52%) [32].Kardas, compared adherence of gliclazide modified release (MR) once-daily to glibenclamide twice daily and found the overall compliance was better in gliclazide MR (93.5%) than glibenclamide (87.2%). Furthermore, 77.6% took ≥90% of doses versus 56.3% of glibenclamide group [33]. Paes *et al* demonstrated adherence rate for patients with diabetes taking a dose once daily to be 79%, 65.6% with twice daily and 38% for the those taking the mediction three times daily [34].

Two studies on Indian patients have also been able to demonstrate the relationship between compliance and frequency of oral antidiabetic agents. Sharma *et al.* studied adherence of patients to anti-diabetic treatment regimens over a period of eight months at the Doon Government Hospital, Uttarakhand. The study found out that non-adherence was highly significantly ($p < 0.001$) associated with frequent dosing. 57.5% of patients who were non-compliant to medication reported multiple dosing as a factor contributing to forgetfulness. More than half of the patients desired a decrease in the number and the frequency of medications [35].

In the study by Rani *et al* in a rural and urban population of Bengaluru, frequency of daily dosage was significantly associated with treatment nonadherence among diabetics. The percentage of noncompliance increased from 38% in once daily dosage to 58% with twice daily dosage ($p<0.05$) [16].

3.2.2 Multiple drugs in the prescription

Multiple drugs were a significant factor for non-adherence in the study by Rani *et al* [16]. Percentage of non-adherence increased from 37.9% with one pill a day to 57.9% with two pills a day ($p<0.001$). Similar findings were reflected by Sharma *et al* in their study wherein 60% of non-compliant patients complained of multiple drugs being a reason for non-adherence to anti-diabetic drugs as compared to 40% who were compliant to medication [35]. The authors of the study further elaborated that fear of inconvenience of daily ingestion of too many drugs is a major hindrance to medication adherence among patients with diabetes. There is a clear need for lesser number of drugs and preferably long-acting ones. An effective way to improve adherence to the anti-diabetic treatment would be to minimise the number of drugs [35].

3.2.3 Side effects

A variety of side effects are reported with antidiabetic medications. The most common side effects are gastrointestinal side effects followed by hypoglycaemic symptoms, weight gain and water retention, constipation or diarrhoea and headaches [36-38]. Patients who experience side effects to their medication are less adherent to the treatment regimen [36]. Several studies have reported side effects to anti-diabetic medications as a reason for non-adherence [39-46]. Similar findings were observed in Indian population too [13,17,47]. Thappar *et al*, concluded absence of side effects was the single most important factor that significantly predicted good adherence behaviour. Side effects in their study was reported in 38% of the study participants that was higher as compared to studies from south of India. The study concluded that although the problem of adherence to anti-diabetes medication is a multifactorial one, absence of side effect was the single most important factor in predicting good adherence and therefore interventions must be targeted towards reducing side effects to increase good adherence behaviour among patients suffering from diabetes [13].

IV. Interventions to Improve Adherence

4.1 Role of Extended-release formulation on adherence

Romley *et al* were the first to investigate the effects of extended-release (XR) medications on long-term (≥ 1 year) adherence across 15 chronic medications, including, metformin and glipizide and concluded that to a degree that was clinically significant, average medication adherence was higher among patients treated with XR formulations [49]. Subsequently Xie *et al* in their study on 29,969 patients using the commercial database, found that patients prescribed XR formulations had improved adherence (78.4% vs. 75.8%, $p< 0.01$) and that the overall adherence would have improved by an additional 5.1% (81.6% vs. 76.5%, $p < 0.01$), had all patients in the sample, used the XR formulations. The study further adds that despite the additional annual cost of $33.55, on using the XR formulations, there was a considerable saving of $470.08 through reduced hospitalizations [48]. A longitudinal study, in France on 4 802 patients with type 2 diabetes revealed an increase in the percentage of patients achieving optimal compliance from 44 to 69.5% after 6 months ($p<0.001$) on having switched from multiple-daily dosing to once-daily-dosing schedules and from gliclazide 80 to gliclazide 30 MR once-daily formulation [52]. A systematic review that compared patient compliance between metformin immediate release (IR) and XR formulations found compliance to metformin XR (80%) to be significantly higher than metformin IR (72%) and that compliance markedly increased after changing from metformin IR (62%) to metformin XR (81%). The review included five randomized controlled trials comprising 1,662 patients and one observational study comprising 10,909 patients. Improved compliance in this review was attributed to patient preference for once-daily administration with metformin XR [50]. A pan-India study that used electronic medical record data to assess the real-world impact of of gliclazide or gliclazide + metformin, in Indian patients with T2DM revealed that the once-daily dosing regimen of extended release formulation of gliclazide, was associated with higher adherence rate (odds ratio [OR] 3.07; 95% CI 1.80, 5.23, $p < 0.001$) and compliance rate (OR 3.50; 95% CI 1.73, 7.08, $p < 0.001$) compared with more than once-daily dosing [54].

4.2 Role of Extended-release formulation on safety

The European GUIDE (GlUcose control in type 2 diabetes: Diamicron MR vs. GLIM) study on 845 noted that hypoglycaemia occurred significantly lesser with extended-release formulation of gliclazide compared to immediate release (3.7% vs. 8.9%, respectively, *P* = 0.003) [53].

Improved tolerance to XR formulation of metformin was also reported in a metanalysis of 15 studies (n = 3765 participants) that found markedly reduced gastrointestinal side effects in patients randomised to longer-acting formulations vs. IR metformin formulations (OR 0.45, 95% CI 0.26–0.80, p = 0.006). This pioneering study compared the two formulations for the likelihood of experiencing each side effect i.e., diarrhoea, vomiting, nausea, abdominal pain/bloating, flatulence, heartburn/dyspepsia, and headache separately and noted reduced likelihood of heartburn/dyspepsia and nausea with longer-acting formulations of metformin. The study firmly concluded that the XR formulation had a better overall tolerability compared to the immediate one. Yet another review study also concluded metformin XR to be associated with significantly fewer adverse events than metformin IR at a 50% lower average maintenance dose (XR 1000 ± 500 mg vs. IR 2000 ± 1,000 mg), suggesting that for most patients receiving metformin XR, up-titration was stopped, much before the maximal dose was reached [50].

4.2   Digital solution to assist in medication adherence

Studies suggest that mobile text messaging are not satisfactory in improving medication adherence. There is a clear need to go beyond basic reminders to improve medication adherence. In contrast smartphone apps can assist people in adhering to their medications. Unfortunately, most apps available in the market today do not possess the useful, desirable features for medication adherence. An assessment on 143 apps suggest that a large proportion suffered from limited medication logging capacity, faulty reminder features, unclear medication adherence assessment and visually distracting excessive advertising thereby adversely affecting their ability in helping users adhere to their medications. Besides healthcare providers are not being involved in the process of app development because of which the apps are not aligned to evidence-based best practice. These gaps represent missed opportunities for better app features, codesigned by healthcare providers, app developers and researchers, which can potentially enhance digital medication management in people with diabetes [55].

V.   Conclusion

Drugs will work in patients only if taken. It is mandatory for patients to follow prescribed treatment regimen to derive the full benefit of medication, especially in chronic conditions like diabetes. However, studies across India have revealed a poor adherence to diabetic mediation. Forgetfulness is one of the major factors cited by patients for noncompliance. Increased frequency of dosing further aggravates the issue of forgetfulness. The other important factor contributing to poor medication adherence is side effects with medication. Studies in India suggest extended-release formulations to improve adherence and reduce side effects with medication. Extended-release formulations can be considered as one of the tools to increase good adherence behaviour among patients suffering from diabetes. Smartphone apps is also a powerful tool in supporting diabetes self-management. There is a need for healthcare providers and app developers to codesign apps with features that are useful in enhancing medication adherence and safety. Diabetes apps that are aligned to evidence-based best practice can further assist people in adhering to their medications.

Declaration of interest
The author reports no conflicts of interest. The author alone is responsible for the content and writing of this article.

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