A systematic review and meta-analysis of non-adherence to anti-diabetic medication: Evidence from low- and middle-income countries

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February 5, 2021

Abstract

Objective: There is lack of evidence on the burden of and factors associated with non-adherence to anti-diabetic medication among individuals living with diabetes in low-and middle-income countries (LMICs). Therefore, we carried out a systematic literature review and meta-analytic synthesis to estimate non-adherence to anti-diabetic medication reported among adults in LMICs and to explore factors affecting non-adherence. Methods: We systematically searched MEDLINE and Embase to identify studies investigating non-adherence to anti-diabetic medications published between January 2000 and May 2020. Cross-sectional studies that had been conducted among individuals with diabetes in LMICs were eligible for the selection process. Critical appraisal of the included studies was carried out using the Newcastle Ottawa Scale. Meta-analysis was carried out using Stata 14.2. Random effects model was used to compute the pooled proportion at 95% confidence interval. Results: Forty-three studies met the inclusion criteria, of which 13 studies were used in meta-analysis. The pooled proportion of non-adherence to anti-diabetic medications using the eight-item Morisky Medication Adherence Scale (MMAS) was 43.4% (95% CI: 17.5–69.4; p=0.000) and 29.1% (95% CI: 19.8–38.4; p=0.000) when using the cut-off at 80 or 90%. The pooled proportion of non-adherence was 29.5% (95% CI: 25.5–33.5; p=0.098) when using the four-item Morisky Medication Adherence Scale. The factors for non-adherence based on World Health Organization demonstrated considerable variation of non-adherence to ant-diabetic medication in LMICs depending on the methods used to estimate non-adherence. Conclusions: These findings demonstrate a significantly higher proportion of medication non-adherence among individuals with diabetes in LMIC settings when MMAS-8 item scale was used and low when 80-90% cut-off scales were used. Various factors, such as disease factors, therapy-related factors, healthcare system factor, patient-centered factors, and social and economic factors contributed to non-adherence. Therefore, comprehensive multifaceted strategies are urgently needed to address factors associated with anti-diabetic medication non-adherence.

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Abstract

Purpose/Objective:

Non-adherence to anti-diabetic medication is an important cause of uncontrolled blood glucose that leads to complications of diabetes. However, there is lack of evidence on the burden of and factors associated with non-adherence to anti-diabetic medication among individuals living with diabetes in low-and middle-income countries (LMICs). Therefore, we carried out a systematic literature review and meta-analytic synthesis to estimate non-adherence to anti-diabetic medication reported among adults in LMICs and to explore factors affecting non-adherence.

Methods:

We systematically searched MEDLINE and Embase to identify studies investigating non-adherence to anti-diabetic medications published between January 2000 and May 2020. Two authors carried out study selection, screening, and data extraction independently. Cross-sectional studies that had been conducted among individuals with diabetes in LMICs were eligible for the selection process. Critical appraisal of the included studies was carried out using the Newcastle Ottawa Scale. Meta-analysis was carried out using Stata 14.2. Random effects model was used to compute the pooled proportion at 95% confidence interval.

Results:

Forty-three studies met the inclusion criteria, of which 13 studies were used in meta-analysis. The pooled proportion of non-adherence to anti-diabetic medications using the eight-item Morisky Medication Adherence Scale (MMAS) was 43.4% (95% CI: 17.5–69.4; p=0.000) and 29.1% (95% CI: 19.8–38.4; p=0.000) when using the cut-off at 80 or 90%. The pooled proportion of non-adherence was 29.5% (95% CI: 25.5–33.5; p=0.098) when using the four-item Morisky Medication Adherence Scale. The factors for non-adherence based on World Health Organization demonstrated considerable variation of non-adherence to ant-diabetic medication in LMICs depending on the methods used to estimate non-adherence.

Conclusions:

These findings demonstrate a significantly higher proportion of medication non-adherence among individuals with diabetes in LMIC settings when MMAS-8 item scale was used and low when 80-90% cut-off scales were used. Various factors, such as disease factors, therapy-related factors, healthcare system factor, patient-centered factors, and social and economic factors contributed to non-adherence. Therefore, comprehensive multifaceted strategies are urgently needed to address factors associated with anti-diabetic medication non-adherence.

Keywords: Medication non-adherence, Diabetes, Systematic Review, Meta-analysis

Introduction

Diabetes is one of the leading causes of morbidity and mortality worldwide. According to the International Diabetes Federation (IDF), 463 million people aged 20-79 years worldwide have diabetes of whom 80% live in low-and middle-income countries (LMICs). This number is projected to increase to 700 million by 2045, and most of the rising burden will occur in LMICs. It is estimated that about half of diabetes cases in LMICs are undiagnosed or poorly treated[1]. Diabetes is associated with an increased risk for a number of serious and sometimes life-threatening vascular complications, including cardiovascular diseases (CVDs), diabetic neuropathy, nephropathy and retinopathy. In fact, CVDs are the most prevalent causes of morbidity and mortality in people with diabetes.

Achieving diabetes control is the ultimate target to prevent or delay early complications of diabetes, which depends on adherence to medications. The World Health Organization (WHO) defines the concept of adherence to medications as the accomplishment of some behaviour, such as taking prescribed medications at the right doses and times in the specified manner as per the recommendation provided by healthcare providers, followed by a lifestyle modification; otherwise, non-adherence exists. For people with diabetes, persistent and compliance with anti-diabetic medication is key to achieving ideal blood glucose levels. Additionally, suboptimal blood glucose control is associated with poor adherence or non-adherence to anti-diabetic medications[2,3]. However, in many developed and developing countries, non-adherence to prescribed anti-diabetic medications remains a serious problem[4]. Rates of non-adherence to prescribed anti-diabetic regimens among individuals with diabetes reportedly ranged from 9% to ¿80%[5]. The non-adherence practice may be particularly higher in LMICs where there is poor accessibility to medicines and healthcare services as well as low level of awareness about the chronic nature of the disease. Indeed, non-adherence to medication contributes to substantial worsening of disease, mortality and increased healthcare cost[3]. Hence, monitoring of medication adherence is of great importance to achieve optimal blood glucose control.

Globally, several screening tools are available for use to assess medication adherence in individual with diabetes, such as Morisky Medication Adherence Scale (MMAS-8), Medication Adherence Rating Scale (MARS), Brief Medication Questionnaire (BMQ), Self-Efficacy for Appropriate Medication Use Scale (SEAMS) and Hill-Bone Compliance Scale (HBCS). However only few scales are designed to assess medication adherence for people with diabetes in LMICs[6]. Furthermore, studies on adherence to diabetes medication are being carried out extensively in developed countries and are scarce in LMICs. The available evidence in LMICs come from single-center studies using various measures of adherence. It became necessary and urgently needed to conduct a systematic review and meta-meta-analysis to understand the burden of and factors of non-adherence to anti-diabetic medication among individuals living with diabetes in LMICs, which is crucial in guiding policy-makers to tailor effective strategies to improve adherence to anti-diabetic medication, and consequently blood glucose control. This study, therefore, aimed to summarize available findings of primary studies to determine the level of anti-diabetic medication non-adherence and associated factors reported in LMICs.

Methods

Data sources and search strategy

This systematic literature review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (supplementary Table S1)[7]. Two databases, including the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Embase were searched using a comprehensive search strategy to identify eligible studies published in the English language from January 2000 to May, 2020. Search terms used were " diabetes mellitus", " type 2/ or hyperglycemia", " noninsulin-dependent diabetes mellitus", " T2D", " T2DM " " type 1 diabetes", "type 1 diabetes mellitus", "insulin-dependent diabetes mellitus", " T1DM", " drug therapy", " medication", " medication adherence", " patient compliance", " developing countries", "low-income", "middle-income", "low income", "middle income", "LMIC", "developing" underdeveloped", "under-developed", "emerging", "less-developed", "least-developed", "less-economically developed", "least-economically developed", "less-affluent", and "least-affluent". Detail tables on the search terms used are provided in the supplementary Table S2**.** Secondary searches that included screening references of the included studies and the previous

systematic review[8] resulted in the identification of an additional 12 eligible studies for full-text screening (Figure 1).

Study selection and data extraction

Two reviewers independently performed the selection of study, which was based on an initial screening of identified titles and abstracts and a second screening of full-text articles. Studies were considered eligible if they met the following criteria: (i) studies reporting anti-diabetic medication non-adherence or adherence and or factors associated with medication non-adherence; (ii) studies using observational study design (cross-sectional); (iii) studies conducted in LMICs as defined by the World Bank [9]; (iv) studies written in English after year of 2000 and (v) published studies which were accessible with full text. We used the following exclusion criteria: studies conducted in high-income countries, studies with no information about adherence/non-adherence to anti-diabetic medications, studies assessing adherence to diet, studies with languages other than English, non-cross-sectional studies, and studies including other types of therapy than allopathic medicine to manage diabetes. Studies with incomplete information or no full text available were also excluded.

Two independent authors performed study screening and data extraction judiciously according to inclusion criteria. Any discrepancies were resolved through discussion of the third author until consent was achieved. A standard data extraction format was used to collect the study information, including name of the first author, year of the publication, country, study design, population, interventions, study settings, sample size, age (years), duration of diabetes (years), adherence measures (self-reported or instruments), response rate (%), proportion of non-adherence to anti-diabetic medication, and where available, odds ratio (ORs) with respective confidence intervals (CIs) for factors associated with adherence/non-adherence.

Measurement of outcome

The main outcome of interest for this review was the proportion of non-adherence to anti-diabetic medication. Medication non-adherence was measured as direct report from studies. Studies used different methods to estimate non-adherence rates. Methods used to estimate non-adherence rates are presented below:

(i) Morisky Medication Adherence Scale:

The Morisky Medication Adherence Scale (MMAS) is a validated assessment tool used to measure non-adherence in a several diseased populations such as CVDs, diabetes, arthritis, musculoskeletal conditions, and mental health. It was originally a four-item questionnaire survey with the dichotomous response categories 'yes' or 'no'. The total score ranges from zero to four, which represents non-adherence and adherence, respectively [10]. In 2008, a modified eight-item questionnaire was developed. The first seven items have a dichotomous response category with 'yes' or 'no', and the last item uses a five-point Likert response scale. The four items added on the modified version aim to identify and address the situational and emotional aspects of medication adherence of the patient[11]. The total score ranges from zero to eight with higher scores reflecting higher adherence and the score less than six denotes that the patient is non-adherent.

(ii) A cut-off at 80 or 90%:

Patients are considered adherent when they take at least 80% of the prescribed medicines and/or agree between the patient and the health care provider for the last one month[12]. The same applies to a 90% cut-off scale.

Quality assessment

Two authors independently assessed the quality of the methodology for each study using the Newcastle-Ottawa scale adapted for cross-sectional studies [13]. The assessment tool comprised of three scales; selection (maximum of five stars), comparability (maximum of two stars), outcome (maximum of three stars) and graded out of 10 points (stars). This assessment critically appraised the internal (systematic error) and external validity of the studies to reduce the risk of biases. The scale is composed of seven items and classifies the study in four possible levels: very good (9-10 points), good (7-8 points), satisfactory (5-6

points) and unsatisfactory (0-4 points). Any disagreement was resolved through consensus (supplementary Table S3).

Data analysis

We carried out meta-analysis using STATA version 14.2 (StataCorp, College Station, TX, USA) and based on the recommendation for the meta-analysis of observational studies. We conducted meta-analysis only among those studies that reported type 2 diabetes. Heterogeneity among studies was assessed with the Cochran chi-square ($\chi 2$) and quantified with the I^2 and tau-square (τ^2) and the values have been mentioned in the text. Substantial heterogeneity was anticipated when I^2 values were greater than 75%. The pooled proportion was estimated using the inverse variance method. Confidence Interval (CI) was estimated at 95% for each proportion. Random effects model was used for the overall pooled estimate meta-analysis. We did not conduct meta-analyses for factors affecting non-adherence, as ORs were reported in less than five dimensions of adherence defined by the WHO, including conditions-related factors, health care system-related factors, social and economic factors, therapy-related factors and patient-related factors[14].

Ethical statement

Ethics committee or institutional review board permission is not required for conducting systematic review and meta-analysis.

Results

Literature search, characteristics, and quality of included studies

As detailed in the flowchart in Figure 1, a total of 3,029 titles/ abstracts were retrieved from the electronic literature and 12 from the bibliographies of published literature. Of these, we independently reviewed 121 full-text articles for eligibility and retained 43 articles for our qualitative synthesis. Only 13 studies were retained for our quantitative data synthesis. The characteristics of the included studies are presented in Table 1. Most (n = 19) studies were conducted in Ethiopia[12,15-32], followed by India (n= 5)[33-37], Nigeria (n= 4)[38-41], Palestine (n= 3)[42-44], one each in Cambodia [45], Cameroon[46], Egypt[47], Indonesia[48], Jordan[49], Malaysia[50], Pakistan[51], Philippines[52], South Africa[53], Tanzania[54], Uganda[55], and one in Nigeria and Ghana [56]. The sample sizes in the included studies ranged from 64 to 773, and the total sample size included for this review was 12,606 (Table 1). The response rates were high in the majority of studies with more than 85%. The high numbers of studies were published in year 2018 followed by 2017 and 2016.

The mean age of the participants ranged from 42.2 ± 6.6 years to 61.1 ± 11.7 years. All studies were conducted in a hospital and primary healthcare setting and only three of the studies were community-based. The majority of the studies (n= 28) were carried-out among individuals with type 2 diabetes[16,19-21,24,26,28,30-32,34,35,37-39,41,43,44,46-48,50,51,53,54,56], four studies were conducted in individuals with both type 1 and type 2 diabetes[15,17,23,40]and the remaining 11 studies simply reported diabetes[12,18,22,25,27,33,36,45,49,52,55].

Several measures were used to estimate non-adherence to anti-diabetic medications; 14 studies used the MMAS-8 scale, six studies used the MMAS-4 and five studies used 80% or above cut-off scales. Table 1 shows that non-adherence to anti-diabetic medications ranged from 3.0% to 68.8%, with the lowest and highest percentage reported in Ethiopia in the year 2017 and 2019, respectively. Moreover, it demonstrated a difference in the non-adherence rate according to the methods used; 32.5% of the studies using the MMAS-8 had a non-adherence rate ranging from 4.6% to 68.8%[15,52]. Only 11.6% of the studies using the self-report/80 or above cut off scales had a non-adherence rate ranging from 17.6% to 38.9%[33,54].

According to the New Castle scale, 16 studies scored between 7 to 8 out of 10, 18 studies scored between 5 to 6, and the remaining nine studies scored 0 to 4, suggesting good, satisfactory and unsatisfactory quality of the studies, respectively (supplementary Table S3).

Magnitude of anti-diabetic medication non-adherence

The pooled proportion of non-adherence to anti-diabetic medication reported in the studies included for meta-analyses are presented in Figures 2-4. The findings showed a considerable heterogeneity. The meta-analyses compared the non-adherence proportions within the five studies using the MMAS-8 (Figure 2), and the non-adherence proportions within the four each study using the MMAS-4 and cut-off at 80 or 90% (Figure 4). The pooled estimates of non-adherence for the studies using the MMAS-8 was 43.4% (95% CI= 17.5-69.4%, I^2= 98.8%, p<0.01). The pooled estimates of non-adherence for the studies using the MMAS-4 was 29.5% (95% CI=25.58-33.5%, I^2= 52.4%, p=0.098) (Figure 3) and for the studies using cut-off at 80 or 90% was 29.1% (95% CI= 19.83-38.4%, I^2= 92.9%, p<0.01), respectively.

Factors associated with anti-diabetic medication non-adherence

Medication non-adherence was influenced by various factors as depicted in the Table 2. We systematically mapped the factors that affect medication non-adherence among individuals with type 2 diabetes according to the WHO's five dimensions of adherence framework-patients related factors, socio-economic-related factors, conditions related factors, therapy-related factors, and health-care systems related factors based on the review of 43 studies.

(i) Patients related factors

One study reported that high body mass index (BMI) was associated with type 2 diabetes [26]. In five studies, patients having poor knowledge of type 2 diabetes were more likely to be non-adherent to their diabetes medication compared to those patients having good knowledge[18,26,32,37,42]. In two studies, low concerns about medication treatment were associated with diabetes medication non-adherence[15,42]. Likewise, two studies reported that low self-efficacy was associated with diabetes medication non-adherence among individuals with type 2 diabetes[32,41].

(ii) Socioeconomic-related factors

Two studies reported that individuals with age group 18-35 years were more likely to be non-adherent to their diabetes medication compared to the age group > 60 years[15,50]. Educational status was one of the influencing factors for medication non-adherence. In four studies, individuals with diabetes having lower education were more likely to be non-adherent to their diabetes medication compared to those patients having higher educational level[25,32,34,35]. Four studies reported that being employed was associated with medication non-adherence[25,32,34,35]. In three studies, it was found that individuals with low income were more likely to be non-adherent to their diabetes medication[17,25,41].

(iii) Condition-related factors

In three studies, individuals having one or more comorbid conditions was associated with diabetes medication non-adherence[15,30,39]. One study reported that having hypertension was associated with anti-diabetic medication non-adherence[37]. Furthermore, having depression was yet another influencing factor of medication non-adherence reported by three studies[15,30,50].

(iv) Therapy-related factors

In three studies, medication side effect was associated with medication non-adherence[25,30,41]. In four studies, complex medication regime was the factor associated with medication non-adherence[18,30-32]. In one study, multiple doses per day was the main cause of non-adherence to anti-diabetic medication[30].

(v) Health-care systems related factors

In two studies, adherence to anti-diabetic medication was associated with dissatisfaction with doctor-patient communication[17,37]. Moreover, poor patient-provider relationship was the factor associated with diabetes medication non-adherence[37].

Discussion

This systematic review and meta-analysis determined the pooled proportion of non-adherence to anti-diabetic medications and synthesized the associated factors with medication non-adherence among individuals with diabetes. Based on the MMAS-8, the MMAS-4, and self-care tools, the proportion of non-adherence to anti-diabetic medication was reported at different ranges. We found the pooled proportion of non-adherence to anti-diabetic medications using the MMAS-8, MMAS-4 and cut-off at 80 or 90% scale was 43.4%, 29.5% and 29.1%, respectively Evidence from previous research reported that the rates of non-adherence to prescribed anti-diabetic regimens among individuals with diabetes ranged from 9% to ¿80% [5], which is in line with current findings. In addition, another review on adherence to medication among individuals with type 2 diabetes reported that average adherence to anti-diabetic medication ranges from 36% to 93%[4]. However, earlier reviews were predominantly focused on adherence with diabetes medication[4,57], factors affecting medication adherence among patients with diabetes[58,59], and economic consequences of mediation adherence in diabetes[60].

Failure to adherence to prescribed medication regime is seen as a serious issue resulting in negative impact on individuals' health and health care system. There is, thus, a need to identify specific barriers that will help in adopting suitable techniques to overcome them and improve medication adherence. Previous studies reported various factors of medication non-adherence among individuals with diabetes, such as the severity of disease, demographic factors and socioeconomic status[58]. This study attempted to collate factors affecting non-adherence from each of the five groups, including disease, therapy, healthcare, patient, and socioeconomic factors, which would have wide generalizability. Results from current study advocates that patient-related factors were consistently related to non-adherence. Patients having high BMI and low concerns were related to non-adherence. Further, non-adherence was consistently associated with socioeconomic factors, such as low education and being employed in our review. Similar findings were also reported in previous studies where association between education and non-adherence reported[25]. It has been reported that low education level can interfere with knowledge of the disease and medication to some extent[26]. Considering potential gap between education and disease awareness, educational research is urgently warranted to identify effective strategies to assist individuals with diabetes in medication adherence.

Patient's knowledge about disease and associated factors could play a pivotal role for better compliance with treatment strategy. This study found that non-adherence was related with condition related characteristics. Individuals suffering from depression was consistently associated with non-adherence to anti-diabetic medication in current study which is in accordance with findings from prior studies[61,62]. For instance, a study by Grenard and colleague reported that individuals with depression were 1.76 more likely to be non-adherent to taking medication for chronic diseases than patients without depression[62]. Therapy-related factor was yet another factor consistently associated with non-adherence in our review. Drug regimen complexity, i.e., taking multiple daily doses was found to be a critical factor for non-adherence to medication. This finding is consistent with that found in a previous review that showed adherence is inversely associated with the number of medication doses per day [63]. This suggests that clinicians should be aware of the fact that access to simplified dosage regimens by patients may be important aspect in maximizing therapeutic success.

Lastly, healthcare system factors were consistently related to non-adherence in our review. We found that poor doctor-patient relationship was associated with medication non-adherence in individuals with diabetes and aligns with findings from a prior review[64], suggesting that doctor-patient relationship quality is a potentially important point of intervention to improve medication adherence. Indeed, the provider-patient relationship plays a major role in keeping the patient well informed about their medications, which directly influences the adherence [65]. In the present study, dissatisfaction with communication was another healthcare system factor associated with non-adherence. This finding is consistent with a prior study about aspects of patient-provider communication and medication adherence in diabetes[66]. Future studies should investigate whether improving communication skills among providers with poorer patient communication ratings could improve their anti-diabetic medication adherence and outcomes. In addition, some factors such as poor knowledge, self-efficacy, young adulthood age, unmarried, low income, having more comorbid conditions, being hypertensive, having adverse side effects and complex medication regime had inconsistent relationships with non-adherence to anti-diabetic medications across studies. Similar results was also reported in

the previous studies[15,37,67].

We used a comprehensive search strategy to identify all eligible studies and attempted to increase the quality of the included studies by using well-defined eligibility criteria. The overall quality of the included studies was acceptable and meeting all the specified criteria. However, current study has some limitation as it was restricted to papers written in the English language only, contributing to potential publication bias. It was not possible to quantitatively pool data from all 43 studies that were identified for the systematic search and this could reduce the generalizability of findings. There was a high heterogeneity between the included studies due to differences in assessment methodologies. Further, we were unable to obtain pooled estimates of the strength of association of each factor. Nevertheless, our extensive summary of the factors associated with non-adherence will be useful when designing interventions to combat non-adherence in future research.

Conclusions

This comprehensive meta-analysis of non-adherence to anti-diabetic medications documented a higher proportion of medication non-adherence among individuals with diabetes in LMIC settings when MMAS-8 item scale was used and low when MMAS-4 and the 80-90% cut-off scales were used. Various factors, such as disease factors, therapy-related factors, healthcare system factor, patient-centered factors, and socio-economic factors contributed to non-adherence. Therefore, multifaceted intervention is needed to create supportive environment for individuals to combat medication non-adherence. Furthermore, given that diabetes is easily controlled by adherence to medication, it is essential to provide trainings and interventional programmes to increase adherence rates in affected individuals.

Conflict of interest

The authors declare no conflict of interests associated with this publication.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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