Review Article

A Systematic Review on Determinants of Adherence to Oral Antidiabetic Agents

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Received: 20-07-2019; **Revised:** 26-08-2019; **Accepted:** 04-09-2019.

ABSTRACT

Diabetes mellitus is one of the leading chronic disease conditions which results in increased risk of morbidity and mortality across the world. Adherence to anti-diabetic agents is essential for achieving a better glycemic control which in turn improve the quality of life of patients. Poor adherence leads to microvascular and macrovascular diabetic complications like diabetic neuropathy, diabetic nephropathy, diabetic retinopathy and cardiovascular diseases. As the treatment of diabetes mellitus requires lifelong adherence, it's management is often a hard task. Factors influencing non adherence includes poor socio-economic status, illiteracy, aging, co-morbidities. We undertook this study to evaluate adherence to oral anti diabetic agents and strategies to overcome non-adherence.

Keywords: Diabetes mellitus, oral anti-diabetics, medication adherence, non adherence.

INTRODUCTION

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin.[15] The cause of diabetes mellitus varies but most commonly due to autoimmune type 1 diabetes or to adult onset type 2 diabetes.[15]

Type 2 diabetes is a more complex condition than type 2 diabetes because there is a combination of resistance to the actions of insulin in liver & muscle together with impaired pancreatic β cell function leading to 'relative' insulin deficiency[15]

A glycosylated haemoglobin (A1c) level can be used to diagnose diabetes, in addition to fasting plasma glucose or oral glucose tolerance test.[16] Each test must be confirmed on a subsequent day[16]

Type 2 diabetes is now being observed in children & adolescents, particularly in some ethinic groups, such as Hispanic and afro-americans[15].

Many cases of type 2 diabetes remain undetected. The prevalence of both types of diabetes varies considering around the world, and is related to differences in genetic & environmental factors [15].

The glycemic treatment goals should be individualized[16]. For patients with short duration of diabetes, long life expectancy of no significant vascular disease a goal closer to an A1c of 6% can be considered[16].

In type 2 diabetes, insulin therapy should be considered any time when the patients A1c is >10%.

The blood glucose must be self monitored regularly by are patients with type 1 or type 2 diabetes mellitus in order to achieve appropriate glycemic control with good adherence

Worldwide the prevalence of diabetes mellitus is on the rise. Systematic analysis of health examination surveys and epidemiological studies with 370 country- years and 2.7 million participants in the year 2011, a diabetes mellitus prevalence study since 1980 showed that more than 347 million people worldwide have been estimated to be diagnosed with diabetes mellitus.[1] According to the studies of world health organization diabetes mellitus will be the 7th leading cause of death by the year 2030 in which majority of cases will be of type 2 diabetes mellitus.[2]

In India according to the Indian council of medical research – India National Diabetes study reports, there are 62.4 million people with type 2 diabetes mellitus and 77 million people with prediabetes. It is expected to be 101 million people by the year 2030. [3]The increase in incidence of type 2 diabetes mellitus has been attributed in part to increasing obesity, sedentary lifestyle, and an increase in minority population.[4]

Medication adherence refers to the extend to which the patients follow the instructions provided to them by the health care provider based on prescribed medicines. Adherence to the prescribed medicines is essential in successful management of chronic disease like diabetes mellitus.[5] Poor glycemic control due to poor medication adherence can result in severe complications like renal failure, cardiovascular diseases, coronary artery diseases, diabetic neuropathy & diabetic retinopathy.[6]

Various studies have also shown that type 2 diabetes mellitus also increases the risk of psychological problems & psychological disorders[7] among adults with type 2

diabetes mellitus occurrence of diabetes related distress (DRD) and depression were found to be more common than other affective disorders (anxiety, panic disorders& dysthymia). [7-8]

Diabetic foot problems comprised foot deformity, comprised foot deformity, current ulcer, amputation, peripheral neuropathy or peripheral vascular disease. [9]

Research evidence suggests that adherence to medication & lifestyle modifications have significant impact on outcome of diabetes treatment & care.

The medication adherence is influenced by several factors which may be patient related, medicine related prescriber related and pharmacy related.[11]

The patient related factors include, age, sex, employment status, educational status, average monthly income, ethinicity, marital status, mode of administration of medication, number of other chronic diseases, forgetfulness, negative attitudes toward the prescriber, negative attitudes to treatment depression [11-13]

Medication adherence may be measured by direct methods and indirect methods. Direct methods include measurement of level of drugs or metabolite in the biological (drug plasma concentration). Indirect methods include, patient questionaires, patient self reports, pill counts, rates of prescription refills, assessment of patient's clinical response, electronic medication monitors, measurement of physiologic markers and patient diaries.[11]

For some studies the indirect measurement of adherence includes medication possession ratio

$$\text{MPR} = \frac{\text{Total number of days supplied}}{\text{Number of days between first \& last refills}}$$

$$\text{PDC} = \frac{\text{Total number of days supplied during an interval}}{\text{Total number of days during that interval}}$$

By using this calculation it is possible to determine the amount of medication the patient received over a period of observation, compared to the ideal amount the patient should have obtained [14].

The measurement of medication adherence using questionnaires includes the use of 4 or 8 item morisky medication adherence scale (MMAS) Or 5 item medication adherence report scale (MARS – 5) [15]

Number of studies are conducted to evaluate the medication adherence of oral anti diabetic drugs using various approaches. The factors influencing non adherence are identified and various measures to be taken to improve the adherence to therapy are detected.

METHODOLOGY

literature search

The research articles included in this review were collected based on library databases, metabolic and endocrine disorders group specialized registers, dissertation and sociological abstracts. The google search engine was used to collect informations. Printouts of various articles were taken and was thoroughly studied. There was no blinding with regard to author or journal.

Study selection

Studies in primary care, secondary care, tertiary care, outpatient, community settings and hospital settings were all included. Prospective observational research studies like cohort studies and cross-sectional surveys were assessed in this review.

Rate of Adherence

A prospective observational study conducted by mudliar et al; in type 2 diabetic out patients attending general medicine department for refill of prescriptions of a secondary care referral hospital in south India with a total of 90 diabetic subjects projected that 83 % of total study participant was non adherent [14].

In this study adherence was measured indirectly using indirect adherence metrics like medication possession ratio (MPR)[14]

Out of 90 patients 43 were male and 47 were females and 33 patients were aged between 61-70 years.

The MPR of non-adherent participants were less than 80%. The study also confirmed that 36% of patients were rehospitalized for diabetic ketoacidosis showing poorest adherence.[14]

According to the research of Shaimol T et.al conducted at outpatient pharmacy of a tertiary care hospital in kerala with 400 type 2 diabetes patients majority of them had shown medium adherence towards oral hypoglycemic agent therapy[17]. Low adherence shown by 35.3% of patients and high adherence were shown by 21.8%of patients, similar to the results published in a study conducted by carlos A prado – Aguilor et al [18] and Geok .H. Yeo et al [19].

A study conducted with 240 patients at kovai medical centre and hospital; Coimbatore Tamilnadu by Mathew, et al; using structured questionnaire conducted that 124 patients were adherent to medication whereas 116 patients were non – adherent [20].

While questionnaire survey using a 5 item medication adherence report scale administered to 382 type 2 diabetes mellitus patients at a public primary care clinic located in sengkang, Singapore estimated that 57.1 % of study population had low medication adherence to at least one of their oral hypoglycemic agent.[21] The study was conducted with 382 patients using a 5 item medication adherence report scale

A cohort study of diabetes patients with 624 men and 518 women visiting a primary care setting in Germany, during the period of October 2008 and march 2010 projected a self-reported non – adherence in 23.8% of patients with only marginal difference between men and women (24.4% and 23.3% respectively).[22]

The study was based on data from the baseline examination of the DIANA study, total 1142 eligible patients with physician diagnosed type 2 DM were analysed[22]. In DIANA study participate completed a self-administered standardized questionnaire (4 item morisky self-report medication adherence questionnaire) at baseline. The blood sample were collected by the recruiting physician and HbA1c was assessed by a central laboratory, using ion exchange high pressure liquid chromatography (G8, Tosch Bioscience) [23].

Classification of glycemic control was based on baseline HbA1c levels defining ≥7.5% as poor glycemic control (PGC) according to the international diabetes federation guideline (23 – 24). The total 20.8% showed poor glycemic control (PGC) According to the international diabetes federation guideline (23-24). In total 20.8% showed poor glycemic control (HbA1c ≥7.5%).[22] among which the PGC was found to be more in men than women (men 23%; women: 18.0%).[22]

Estimation of therapeutic adherence by a prospective drug utilization study of oral hypoglycemic in 184 diabetes patients visiting the out patient department of majeedia hospital, New delhi, India was conducted by GulamHaider Khan, et al and conducted that only 48. 3% of the study population showed good adherence with the prescribed therapy, which was estimated by using 4 item morisky medication adherence report scale. [24]

A descriptive cross section study by Khaled heissam, et al, at Fanara family medicine center, Suez canal university, Egypt assessed patterns and obstacles to adherence to oral hypoglycemic drugs by type 2 diabetic patients I the year 2014.[25] the adherence was assessed by using questions of the Measure Treatment Adherence Scale (MTA) scale developed by Delgado and Lima. [25]

A total of 372 patients were included in the study among them 26.1% were found to have good adherence, 47.9% had fair adherence and 26% of participants had poor adherence .[25]

According to Sontakke, et al data obtained from the self developed questionnaire showed that 70% patient were non adherent to the medication schedule, patients lack of knowledge, poor affordability and forgetfulness are the major causes of non adherence .[5]

From the study conducted by Jackson et. al only 19.8% of the patients were adjudged highly adherent to their anidiabetes medications.[11]

FACTORS INFLUENCING ADHERENCE

Gender

Most of the studies projected better adherence in males compared to females. The study by Shaimol.T et.al, suggested that males showed better adherence (24%) than females (20.8%).[17]

Age

According to most of the studies age below 40 showed better adherence compared to older age, this may be due to increased co morbidities and medications with increase in age, and poor memory can also result in poor adherence.

From the study conducted by Sontakke et al male gender was found to be associated with better adherence than the female patients[5].

Educational status

The studies suggests that the individuals with secondary, higher secondary education and graduates showed better adherence compared to illeterates individuals with only primary education.

This may be because people with better knowledge about disease and medication showed better adherence, compared to people who do not have much knowledge about disease and medications.[26]

Income

The category of people with low income showed poor adherence compared to individuals with average or good income.

The medication adherence study of Shaimol T et al, showed that 30.9% of patients under APL category show high adherence compared to 20.9% of patients under BPL category. [14]

Number of drugs

Significant difference in rate of adherence was not found in polytherapy. Patients taking five or more daily medications summed to be more adherent to their antidiabetic drugs according to the study of Leels, etal .[12]

The study of Shaimol T et al reported high adherence in 19.7% of patients on monotherapy and a high adherence in 24 % of patients on monotherapy and a high adherence in24% of patients on poly therapy. [14]

From the study conducted by Sontakke et al patients under monotherapeutic treatment with sulfonylurea or metformin had about 65% more adherent days than did patients treated with combination therapy.[5]

INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

The adherence to medications by the patient is influenced by various factors. To improve the medication adherence properly it is better first identify the cause of non adherence and take measures accordingly to improve the adherence.

There are some common measures that can be taken to improve adherence based on some common factors resulting in non adherence.

Set up reminders or pill dispensers

One of the main reason for non adherence is forgetting to take the medicine, this can be avoided by setting reminders to take medicines.

Health IT presents various opportunities for patients to remember and manage medicines like chronic self-management apps which send reminders to patients to take their daily pills.

But this method will be difficult for elderly patients and patients with poor socioeconomic background.

Other methods include utilizing sticky notes as reminders. The patients should follow patterns like keeping their medicines near to the breakfast table or where they can see and remember to take.

Medication synchronization is useful for patients managing multiple medications. [27]

A standard pill box with compartments for each day of the week will be helpful to organize the medications and it is possible for the patient to immediately recognize if he or she did not take the medicine. [28]

Encourage patients to keep a medication list

Encourage patients to keep a list of the medications they take including the name, dose, dosage form and frequency of the medicine. Advice the patients to give a copy of this to the physician and care taker in case of an emergency.

Keeping a record of medications one take is always helpful.[28]

Educate patient and enhance regimen recall

Verify patients understanding while in the clinic and clarify doubts regarding the regimen if present. Use visual aids to enhance the understanding of the patient. Give sufficient information to the patient regarding the disease, treatment regimen and the importance of medication adherence. [27 -28]

Minimize cost

One of the major barrier for medication non adherence in patients with poor socioeconomic background is high cost of medicines. Develop cost cutting strategies. Change regimen when appropriate and encourage using free government medical services.

Some patients are reluctant to admit that they have financial difficulties, it is the responsibility of the health care provider to identify if the patient is having financial problems by asking questions to the patients like if they are taking pills regularly, how they are getting them, where they are getting them.

If a cost barrier is discovered the health care provider must work with the patient and develop most accommodating treatment strategy for the patient. [27- 28]

Minimize and manage adverse effects and side effects

One of the reason for patients not taking the medication is because they experience side effects or adverse effects. This problem should be identified as early as possible and measures should be taken to reduce such problems. Proper monitoring of the patient's treatment must be performed and appropriate changes in the regimen must be made. [27- 28]

Identify and overcome mental barriers

The mental barriers varies among the patients. Some studies found that the adolescent patients were resistant to take medications in front of their peers. Some patients do not fully believe in medicines, due to this reason they do not follow the treatment properly. [27- 28]

CONCLUSION

The rate of adherence is less compared to the rate of non-adherence. The non-adherence was found to be more common in elderly patients, illiterate patients and patients with poor socioeconomic status. The non-adherence to antidiabetic agents results in poor glycemic control leading to diabetic complications. The adherence can be improved by educating the patients on disease and therapy. Maintaining a good collaborative relationship between patients and providers can encourage the patient to follow up on therapy and thus increase the adherence rate.

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Source of Support: Nil, **Conflict of Interest:** None.