

# T2DM Patients Adherence Towards OAD Medication: A Literature Review

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## Abstract

Type 2 diabetes mellitus (T2DM) defined as a disease in metabolic, known with increased levels of blood glucose caused by insulin resistance. The etiology of T2DM causing hyperglycemia is a built up from a multifactorial complex process, starting from insulin resistance alongside relative insulin deficiency developing into predominant insulin secretory defect alongside with insulin resistance. It is acting as an international obstacle. Patients are treated by consuming medications targeting glycemic control. However, poor adherence in diabetes is known to be one of the main problems. Patient's adherence could be affected by many factors both external and internal. It could be viewed as the patient's willingness to follow the health care instructions to manage the disease. This article aims to review studies regarding T2DM patient's adherence towards OAD.

Keywords: type 2 diabetes mellitus, adherence, OAD, literature review

## 1. Introduction

Diabetes mellitus (DM) is a metabolic disease, with chronic clinical manifestations of increase blood glucose's level resulting from limitation of insulin secretion, action or both [1]. It is acting as an international obstacle as stated by IDF in 2019, as much as 463.0 million 20-79-year-old all around the world suffered from diabetes. The prevalence was thought to be 9.3%. Type 2 Diabetes covered 90% of all the total diabetes case. The number is thought to be increased to 578.4 million with global prevalence of 10.2% by the year of 2030 [2]. Diabetes has a great impact in patients' life starting from costs of medications, complications altogether with poor quality of life [3].

Type 2 diabetes mellitus' (T2DM) patients are treated by consuming medications targeting glycemic control. However, poor adherence in diabetes is known to be one of the main problems as it is widely spread and studied on several previous study. At least 45% of total patients are thought to not be able to be on track with medication adherence [3].

Patient's adherence could be affected by many factors both external and internal. It could be viewed as the patient's willingness to follow the health care instructions to manage the disease. Factors such as disease characteristics, intra-personal, inter-personal and environmental do affect one's adherence [4]. As the data shown above, the adherence of T2DM patients towards DMT2 OAD medication is important to be studied to gather the latest knowledge of it. Thus, this study aimed to review literature and previous studies about patient's adherence towards DMT2 OAD medication.

## 2. Overview of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is classified as a disease in metabolic, known with increased levels of blood glucose caused by insulin resistance [1]. It is defined as a situation where the cells of

the body don't act upon the effect of insulin, causing increased level of insulin, but as it progressed, insulin secretion cannot maintain the homeostasis of the glucose causing hyperglycemia. It's often called as adult-onset diabetes [5].

### Etiology

The etiology of T2DM causing hyperglycemia is a built up from a multifactorial complex process, starting from insulin resistance alongside relative insulin deficiency developing into predominant insulin secretory defect alongside with insulin resistance [6]. Predominantly it affected people aged 45 years old and older, but due to increased numbers of obesity, sedentary lifestyles, and high-carb diets, it is increasingly seen in young adults and children [5].

### Pathophysiology

Pathophysiology of T2DM involves factors from genetic predisposition and environment's triggers [7]. The core of the disease is impaired of insulin secretion.  $\beta$ - cell dysfunction played a big role in T2DM. There will be decreased uptake of glucose by peripheral muscle tissues and the hepatic glucose production (HGP) will be increased secondary to the heighten gluconeogenesis [7]. At first, the  $\beta$ -cell will compensate by increasing insulin secretion in order to try maintaining the glucose levels in normal level. As it progresses, beta cells wouldn't be able to keep up, and insulin secretion will not be able to maintain the homeostasis of the glucose resulting in hyperglycemia [5].

T2DM manifested an increase in  $\alpha$ -cells in pancreas, glucagon secretion and sensitivity of hepatic to glucagon. By stimulating hepatic glucose production (HGP), glucagon helps to maintain glucose homeostasis by counteracting the effect of insulin's suppression of HGP. Increased sensitivity to the stimulatory impact of glucagon on HGP is also a result of this process [7].

T2DM's pathophysiology also involves the kidney. Whereas in a hyperglycemic state, the kidney is anticipated to reply by excreting the overly filtered glucose. When glucose reabsorption is improved in T2DM, however, the kidney instead retains glucose. The septicidal septet is a term used frequently to describe this kidney involvement in the etiology of T2DM [8].

Last but not least, the pathogenesis is influenced by the brain's involvement in altered neurotransmitter dysfunction. In a healthy state, insulin would tell the brain to cease eating and to stifle the appetite. In spite of the hyperinsulinemia state, food consumption is still elevated in fat people. These occurrences support the idea that the brain has insulin resistance [8]. These eight pathologies of T2DM are referred to as the frightening octet.

### Risk Factors

These are some risk factors of T2DM according to American Diabetes Association [1] [9] [10] [11]; [12]:

- Family history of diabetes  
Family history in first-or second- degree relatives often affected T2DM, but the exact genetics knowledge is still not fully known.
- Overweight or obese  
Most of the patients are predominantly have higher body fat percentage, and predominantly distributed in the abdomen region, which made the individuals prone to T2DM. The adipose tissue will trigger various inflammatory process, resulting in increasing insulin resistance, free fatty acids (FFA) release and dysregulation of adipokine [5].
- Physical inactivity
- Race/ethnicity:  
Native American, African American, Hispanics, Asian American Pacific Islander
- Previously tested with IFG, hemoglobin A1c (HbA1c) or IGT of 5.7%-6.4%.

- History of gestational diabetes mellitus (GDM)
- Hypertension
- Polycystic ovary syndrome (PCOS) or acanthosis nigricans
- History of cardiovascular disease

### Clinical Manifestations

Patients are most likely seen with increased thirst, poly urination, malaise, infections of bacteria and fungus, and prolonged healing of the wound. Some patients might [13]complain experiencing numbness, or tingling on both extremities in hands and legs, alongside with blurred vision [5].

### Complications

Complications in T2DM can happen both acute and chronic. Hypoglycemia, diabetic ketoacidosis, hyperosmolar state hyperglycemic associated, and diabetic coma hyperglycemic associated are examples of acute complications of diabetes, whereas chronic complications could cover from coronary artery disease (CAD), nephropathy, retinopathy and neuropathy, peripheral artery disease (PAD) and cerebrovascular disease [13].

### Managements

The foundation of therapy for T2DM patients consists of a number of crucial components that are interconnected. These include a personalized glycemic control strategy, care for accompanying illnesses, and monitoring and control of potential consequences from diabetes [6]. The general objectives of treating T2DM are to reduce the risk of long-term microvascular and macrovascular complications, eradicate symptoms associated with hyperglycemia, and preserve patient quality of life [14]

Diabetes education, nutrition management, lifestyle adjustments, physical activity or exercise, and pharmacological intervention are the cornerstones of customized glycemic control for T2DM [15] Diabetes education is crucial because individualized treatment objectives and tactics need careful consideration of patient wants and needs, which calls for diabetes education. The process of supporting the information, skill, and capacity required for diabetic self-care is known as diabetes self-management education (DSME) [16]

Diet management or like to be called as medical nutrition therapy (MNT) are aimed to introduce the patients into eating healthy lifestyle to achieve and maintain the ideal body weight alongside with addressing each patients' nutritional needs [17]

Exercise has several benefits, including lowering blood pressure and cardiovascular risk, reducing body fat, and promoting weight reduction [6]. Adults with T2DM were advised by the ADA to engage in resistance and aerobic exercise for best glycemic control. Exercise should be performed every day or without breaks for at least two days.

Drug therapy for T2DM patients is limited to glucose-lowering medications that focus on several pathophysiological pathways. The pharmacological treatment might be administered orally or intravenously. OAD is classified as an insulin secretagogue, alpha-glucosidase inhibitor, insulin sensitizer, dipeptidyl peptidase (DPP)-4 inhibitor, and an insulin secretagogue (sulfonylurea). In the meanwhile, there are insulin and GLP-1 receptor agonists for injection.

The following are possible drug [18]:

1. Mono therapy  
Given to T2DM patients with HbA1C levels between 7.5% and 9.0% along with advice on adopting a healthy lifestyle
2. Dual Therapy  
Given without first completing monotherapy when HbA1C cannot be brought down to the desired level of 7% within three months or if it has been >9% since the beginning. consists of a first-line medication with a medication with a different mode of action.
3. Triple therapy  
Given if two-drug combinations fail to attain the aim of the control. Figure 2 showed the medication combination selection. 6.
4. Basal insulin plus/bolus or premix  
Administered if the three medication combinations fail to attain the target for the control.
5. Combination injectable therapies  
If a patient has metabolic symptoms and an initial HbA1C level of more than 10.0% or random plasma glucose greater than 300 mg/dL

### 3. Treatment Adherence

Adherence might be defined as the degree to which a patient is willing to follow the management recommendations made by a healthcare professional. Adherence in T2DM patients can be divided into adherence to medicine, following dietary advice, increasing physical activity, controlling blood sugar on one's own, and taking good care of one's legs [19]

#### Factor Contributing to Treatment Adherence and Non-adherence

The factor that are thought to be correlated with adherence in diabetes patients are treatment and illness features, intrapersonal factors, interpersonal factors, and environmental factors, according to WHO publications on the multi-factorial of nonadherence to long-term therapy [4].

##### 1. Disease symptoms and managements

The following elements are linked to this variable:

###### - Complexity of therapy

The number of medications and the frequency of doses might be used to simply describe the complexity of a pharmaceutical regimen, but other people believed that dosing forms and extra instructions also contributed to its complexity [20]. Pharmaceutical adherence is thought to be hampered by medication complexity and numerous daily dose schedules [21]

The complexity of diabetes therapy has a detrimental influence on adherence, which leads to poor glycemic control, according to study that examines how T2DM patients taking OAD respond to treatment complexity [22]. Another study done in Ethiopia revealed that patients with low and intermediate regimen complexity had better adherence, whereas those with high complexity of their diabetes-specific pharmaceutical regimen had worse glucose control [20].

A study measuring the oral medicine adherence of T2DM patients to hypoglycemic, antihypertensive, lipid-lowering, and/or antiplatelet treatments both individually and together revealed that 35.4% of patients had satisfactory adherence to all drugs [23].

###### - Pill burden

T2DM is frequently diagnosed in conjunction with other illnesses, which increases the number of medications and pill load [24]. In order to treat their hyperglycemia, diabetes-related illnesses, and other comorbidities, T2DM patients frequently need to take many medications.

Pill load, also known as total daily pill burden, is the total number of pills a patient takes daily. It is calculated by adding the daily dosages of all oral medications used for treating related disorders as well as blood glucose control therapy [25].

In Scotland, Donnan studied the compliance of people with type 2 diabetes in the entire community. His findings revealed that the number of pills taken each day and the number of co-medications were both related to lower compliance [26]. Similar findings were found in a more recent research conducted in Germany in 2015 concerning the burden of pills for people with type 2 diabetes [25]. In that study, 52.2% of the individuals used three to six tablets daily, with 55.6% of them being under 65 and 48.9% being over 65 [25].

The overall pill load was positively correlated with adherence, with each additional tablet a patient took per day increasing adherence to antidiabetic drugs by 22%, according to a research examining the factors influencing oral antidiabetic medication adherence in U.S. adults with T2DM [24].

- Duration of disease

An earlier study on adherence in diabetic patients revealed a weak correlation between adherence and the length of the illness. According to WHO reports on the multifaceted causes of nonadherence to long-term therapies published in 2003, the length of the disease appears to have a negative relationship with adherence, meaning that patients who have had diabetes for a longer period of time are less likely to adhere to treatment [4].

However, studies regarding diabetes patients from all 50 states as well as the major U.S. territories like Puerto Rico, the Virgin Islands, and Guam revealed that patients who were just starting therapy were 61% less likely to take their diabetic medicine consistently [24].

Additionally, a research on medication compliance in T2DM patients carried out in a population-based environment in France revealed that the time from diagnosis had no effect on medication compliance [27]. A more recent study with similar findings was carried out in East Java, Indonesia's Jombang District Hospital. The findings revealed that there is no significant correlation between the length of the illness and adherence to long-term drug therapy [28].

## 2. Intra-personal factors

- Age

Age was not significantly correlated with adherence in the first research of T2DM patients in a large community, which was conducted by Donnan in Scotland [26]. A similar outcome was also observed in a research carried out in Uganda [29].

However, more recent studies on the factors influencing diabetes medication adherence in American settings revealed that adherence was probably correlated with older age, with patients aged 25 to 44 having a 49% lower likelihood of being compliant than those aged 45 to 64. [24]. This conclusion is in line with a research by Curkendall on factors predicting medication adherence in T2DM patients, which revealed that adherence was greater among those 65 and older (53.7%) [30].

- Gender

There are no meaningful distinctions in adherence between males and females, according to a study on T2DM patients' adherence conducted by Donnan in Scotland [26]. According to a study, adherence to T2DM therapy is not influenced by gender ( $p$ -value= 0.61). [31]. A French population-based study on medication adherence in T2DM found similar results, with the study finding that gender had no impact on medication adherence (Tiv, 2012). However, a more recent study found that men were more likely to be adherent than women, with male adherence being greater (58.2%). [30].

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- Education level

Higher educational levels were found in a research on adherence in T2DM patients that was carried out in East Jakarta, Indonesia. The majority of participants had graduated from senior high school (36.6%)[32]. The majority of participants in another trial with a comparable background that focused on adherence for T2DM patients and was carried out at an Ethiopian general hospital had lower educational levels (46.5%). [20].

3. Inter-personal factors

Social support and the degree of the patient-provider relationship's quality are factors connected to this characteristic.

- The interaction between patients and healthcare professionals

A study of T2DM patients' adherence in a French population-based research revealed that decisions made by the patient alone, a lack of acceptance of medical advice, and physician follow-up were all strongly correlated with poor adherence [27].

There was no difference in adherence between individuals with primary care and endocrinologist prescribers, according to the findings of another study conducted in American settings. Patients who were prescribed medication by non-endocrinology specialists had somewhat decreased odds of adhering, despite the fact that specialty was independently related with adherence [24].

- Social support

Lack of family or social support and taking medications alone were found to be important risk factors for poor drug adherence in a French population-based research on T2DM treatment [27]. Accordingly, a qualitative study conducted in Qatar discovered that social pressure and diabetes stigma were often mentioned as obstacles to medication adherence by both patients and healthcare professionals [33]

4. Environmental factors

High-risk circumstances and environmental factors are connected to this variable, and these factors have been connected to low adherence in diabetic patients [4]

A cross-sectional, population-based investigation on the relationship between neighborhood traits and adherence to diabetic self-management practices in T2DM California adults revealed that neighborhood safety was connected to treatment nonadherence. Whereas respondents who reported feeling comfortable in their neighborhood reported a lower percentage of delays in getting their prescriptions filled than those who reported living in risky communities [34].

Societal and environmental variables were identified as obstacles to diabetes patients' adherence to their medication in a qualitative research conducted in Qatar [33].

#### Evaluation of Adherence Level Using Morisky Medication Adherence Scale (MMAS-8)

Measuring patient medication compliance may be done in 2 different ways: directly and indirectly [35]. The direct technique involves observing the drug or its metabolite levels in the blood or urine and identifying or quantifying biologic indicators in the blood. The direct approach, however, has the drawback of being costly and time-consuming. Patients are questioned about their drug use, clinical response is evaluated, pill counts, prescription refill rates are calculated, and a questionnaire scale is used in the indirect technique.

Brief Medication Questionnaire, Hill-Bone Compliance Scale, Eight-Item Morisky Medication Adherence Scale, Medication Adherence Questionnaire, Self-Efficacy for Appropriate Medication Use Scale, and 7.3.6 are a few examples of questionnaires and scales that could be used to measure



medication adherence indirectly (MARS). In comparison to the MAQ, the MMAS-8 shows superior validity and reliability values in patients with chronic illness [36]

The MMAS-8 questionnaire has four domains or features of items. For questions 1-4, the first domain is whether the patient took or forgot their prescription. The second area or aspect relates to ceasing drug use for items 3 and 6. The third area of concern is whether taking medicine disturbs item number 7. For item number 8, forgetfulness about drug administration is the last sector or element. Yes/no responses are accepted for each of the first seven items, and the last item accepts responses on a 5-point Likert scale. After the questionnaire is completed, the score is divided into 3 adherence groups. If the overall score is greater than 8, moderate adherence is indicated by a score between 6 and 8, and low adherence is indicated by a score below 6 [37].

#### Levels of Treatment Adherence to OAD Medication in Previous Study

Several prior studies have examined the rate of treatment adherence to OAD medication. For instance, DiMatteo did a meta-analysis of 569 studies on adherence across a variety of medical illnesses in 2004. The average adherence rate for diabetes was shown as being among the lowest. According to this study, cancer, arthritis, gastrointestinal illnesses, and HIV disease had the greatest rates of adherence. In contrast, adherence is lowest in cases of diabetes, pulmonary illness, and sleep disturbances [38].

In 2008, Cramer did a review of the literature based on 139 research on patient adherence to or persistence with cardiovascular or anti-diabetic therapy. In this study, adherence is assessed by the mean medication possession (MPR) ratio, and compliance is utilized as a synonym for adherence. A MPR of more than 80% is sometimes regarded as adherence. It is calculated as the number of treatment days administered divided by the number of days between prescription renewals (excluding the latest prescription). According to this study, only 58% of patients used OADs for more than 80% of the days they were "on therapy" during the year [39].

Nanda carried out a case control research at the Mojo, Pucang Sawu, and Keputih Primary Health Care Centers in Surabaya. The study's samples include female respondents with diabetes mellitus aged 45 to 59, who were split into two groups: the case group (patients with uncontrolled blood glucose levels), and the control group (patient with regulated blood glucose). Only 46.2% of diabetes patients in the uncontrolled blood glucose group adhered to their treatment regimen, and the remaining 53.8% did not. In contrast, 92.3% of people in the regulated blood glucose category adhered to their anti-diabetic medication regimen, and 7.7% did not [40].

Another cross-sectional study of T2DM patients at the Kedurus Primary Health Care Center in Surabaya revealed a similarly low percentage of adherence. MMAS-8 in particular reveals that just 18.20% of individuals had good adherence, 24.20% had moderate adherence, and 576.0% had low adherence to their prescriptions. Consequently, just 25 percent of the participants take their prescription as prescribed [41]

#### Reasons for Non-Adherence Towards OAD

Studies conducted by doing cross-sectional method of T2DM patients in East Jakarta located at the Public Health Center, was assessed using MMAS-8. It showed all subjects distributed in moderate and low adherence (45.1%) forgot to take or inject the OAD as their main reason for non-adherence, not consuming OAD for the last 2 weeks (30.9%), reduced consummation of OAD without informing the healthcare professional due to worsen feeling when taking or injecting the medication (7.4%), forgot to bring the medication when travelling (22.3%), did not use the OAD before filling the MMAS-8 (11.4%), inconsistently stopping or not using the drugs because already feel better (10.3%), disturbed by the habit of taking antidiabetic medication (10.3%). Concluded that forgot to take or inject the medication is the main reason for the non-adherence [32].

In a case-control study of T2DM patients carried out in three Primary Health Care Centers in Surabaya, the reasons for non-adherence were revealed (Mojo, Pucang Sawu, and Keputih). Using MMAS-8, it can be seen that subjects intentionally abstaining from taking their medications (38.5%), intentionally forgetting to take their medications (69.2%), unintentionally forgetting to take their medications when leaving the house (46.2%), unintentionally forgetting to take their medications on the day the interview was conducted (15.4%), unintentionally forgetting to take their medications (23.1%), and medication refusal are the main causes of non-adherence in the uncontrolled blood sugar group. This indicates that participants forgetting to take their medication accounts for the majority of non-adherence (69.2%) [40].

Because most of the individuals in this research were elderly and took a lot of pills each day, forgetfulness may have been the major cause of non-adherence. Most senior T2DM patients have trouble managing their oral prescriptions on their own. Medication alone and a lack of family or social support were thought to be substantial risk factors for poor adherence [27]. Therefore, having a family member who might aid with reminding them of their drug regimen may help with medication adherence.

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