

Medication Adherence in Patients with Diabetes and Dyslipidemia: Associated Factors and Strategies for Improvement

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Abstract Dyslipidemia and diabetes mellitus are commonly coincident, and together contribute to the development of atherosclerotic disease. Medication therapy is the mainstay of treatment for dyslipidemia. Optimal medication therapy for dyslipidemia in patients with diabetes reduces cardiovascular events but necessitates patients take multiple medications. As a result, sub-optimal adherence to medication therapy is common. Factors contributing to medication non-adherence in patients taking multiple medications are complex and can be grouped into patient-, social and economic-, medication therapy-, and health provider and health system-related factors. Strategies aimed at improving medication adherence may target the patient, health care providers, or health systems. Recent data suggest medication non-adherence contributes to racial health disparities. In addition, health literacy, cost-related medication non-adherence, and patient beliefs regarding medication therapy have all been recently described as factors affecting medication adherence. Data from within the last year support an important role for regular contact between patients and health care providers to effectively address these factors. Cost-related barriers to medication adherence have recently been addressed through examination of health system approaches to decreasing cost-related non-adherence.

Keywords Medication non-adherence · Diabetes mellitus · Dyslipidemia

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Introduction

Dyslipidemia is common in patients with diabetes mellitus (DM) and contributes to the development of atherosclerotic disease [1]. Medication therapy, primarily with statins, is the mainstay of treatment of dyslipidemia and reduces the rate of cardiovascular events in diabetics [2, 3]. Optimal medication therapy for patients with coincident diabetes and dyslipidemia requires multiple medications including statins and oral anti-hyperglycemics, but this need for multiple medications also leads to higher rates of non-adherence [4, 5]. This article will review both early and more recent studies describing the factors associated with non-adherence to medications in patients taking multiple drugs. It will use these as context to review prior and recent data regarding methods to improve medication adherence in patients with dyslipidemia and diabetes and suggest directions for future research.

Factors Associated with Non-Adherence

The construct of adherence has been variably defined and has evolved over time. For the purposes of this review, adherence is defined as “the extent to which a person’s behavior... corresponds with agreed recommendations from a health care provider [6].” Medication taking is a complex phenomenon, and patients with dyslipidemia and diabetes mellitus face multiple barriers to medication adherence. Factors associated with adherence can be grouped into social and economic-related factors, therapy-related factors, patient-related factors, and health provider and health system-related factors (Table 1).

Table 1 Factors associated with medication adherence in patients taking multiple medications

Social and economic-related factors	Race
	Age
	Economic cost of medication therapy
Medication therapy-related factors	Dosing frequency
	Medication side-effects
	Patient perceptions of medication risk and benefit
Patient-related factors	Level of health literacy
	Alcohol use
	Severity and complexity of medical illness
Health care provider and health system-related factors	Quality of communication between patient and health care provider

Medication Adherence in Patients with Multiple Medical Conditions

The management of multiple coincident chronic medical conditions can be challenging for patients and health-care providers. Adherence to medication therapy is an important component of control of multiple chronic diseases. A recent analysis described the incidence of simultaneous control of hyperglycemia, blood pressure, and low-density lipoprotein (LDL) cholesterol in patients with diabetes mellitus, hypertension, and dyslipidemia from two health systems [7•]. In this cohort, achievement of simultaneous control of all three conditions was more likely as medication adherence increased, but the overall rates of simultaneous control were low. Over a 4-year period, 16 % of patients in one health system and 30 % in the other had simultaneous control of all three conditions defined as a glycosylated hemoglobin (HgbA1c) <7 %, blood pressure <130/80 mm Hg, and LDL < 100 mg/dL (< 2.5 mmol/L).

Adherence to statin therapy in patients with diabetes mellitus also taking oral anti-hyperglycemic medications is often poor. A retrospective analysis of claims data for over 52,000 patients with type 2 diabetes mellitus who were prescribed both a statin and an oral anti-hyperglycemic medication examined the adherence to concomitant statin and oral anti-hyperglycemic therapy [5]. The authors compared the 2-year medication possession ratio (MPR) between statin and oral anti-hyperglycemic therapy. An MPR \geq 80 % was considered adherent. Two years following the initial prescription, the proportion of patients with \geq 80 % MPR was 52 % for statin therapy and 63 % for oral anti-hyperglycemic therapy.

Social and Economic-Related Factors

Social and economic factors influence the rate of adherence to multiple medications in patients with chronic conditions. Socio-economic status and length of education have been associated with medication adherence in patients without diabetes mellitus

[8]. Data regarding the effect of socioeconomic status are lacking in those with diabetes. However, race, age, and economic cost of medical therapy have been associated with rates of medication adherence in patients with diabetes mellitus.

Race has been associated with disparities in the medical management of dyslipidemia in diabetics, and recent data suggest this may in part be due to rates of medication adherence. In a prospective study of 11,411 patients with diabetes and dyslipidemia, African American patients, as compared to Caucasians, were less likely to be tested for LDL, treated with lipid-lowering agents, or attain goal LDL levels [9]. In a separate study, Caucasian ethnicity was associated with higher rates of simultaneous control of diabetes, dyslipidemia, and hypertension [7•]. The mechanisms underlying these disparities are complex and remain poorly defined, but a recent study suggests differing rates of adherence may partially explain racial disparities in the management of chronic diseases including diabetes mellitus [10]. In this study, African American race was associated with higher rates of self-reported non-adherence to medications for coronary heart disease, diabetes mellitus, and hypertension. Further, data from a recent Veterans Affairs analysis suggest race is associated with medication adherence and this association may effect outcomes in patients with diabetes [11]. These data suggest a complex relationship between race and medication adherence in patients with diabetes mellitus. The mechanisms underlying the associations between race and medication adherence remain unclear. However, recent data suggest differences in rates of medication adherence contribute to disparities in outcomes among racial groups with diabetes. A greater understanding of the mechanisms of racial disparities and medication adherence is needed to target interventions aimed at improving medication adherence in all patients.

There are conflicting data regarding the association between age and adherence to multiple medications. A number of studies have examined the adherence to medications for secondary prevention of myocardial infarction (MI) and noted an inconsistent association with age [12, 13]. More recently, an analysis of medical and pharmacy data for post-MI patients noted increased rates of non-adherence associated with older age [14]. While these data provide some insight into the relationship of age and medication adherence, it is unclear how they may apply to patients with diabetes mellitus without MI. A recent survey of adherence rates in patients with diabetes mellitus and hypertension provides more data [15]. In this study, age older than 55 was an independent predictor of higher medication adherence rates. The varying degree to which age has been associated with medication adherence suggests other variables associated with age may be independently associated with adherence. Further work to delineate the relationship of age with medication adherence will need to focus on those factors that are unequally distributed between age groups and influence medication adherence. Possible confounding factors include insurance

status, socioeconomic class, number of co-morbidities, and complexity of medical regimen.

The impact of the cost of medications on adherence in post-MI patients was investigated in the MI-FREEE trial [16]. The trial randomized 5855 post-MI patients, 2023 of whom had diabetes mellitus, to either the usual prescription coverage or to full prescription coverage for all statins, beta-blockers, angiotensin-converting-enzyme inhibitors, or angiotensin-receptor blockers. There was no significant between-group difference in the rate of the primary end-point of the trial, a composite of first major vascular event or revascularization. However, adherence rates for all three medication classes were 5.4 % higher in the full coverage arm than in the usual coverage arm. In addition, the odds of full adherence to all study medications were increased by 31–41 % in the full coverage arm of the trial.

The incidence of cost-related non-adherence in patients with diabetes was recently described in a study conducted with computer-assisted telephone interviews. Of the over 1200 patients with diabetes who were Medicare Part D beneficiaries, approximately 16 % reported cost-related non-adherence [17]. Cost-related non-adherence was noted to be more frequent for lipid-lowering medications. These data suggest medication cost is an important factor affecting medication adherence. Strategies to decrease the impact of cost-related non-adherence in patients with diabetes and dyslipidemia will need to be sustainable for years. While the increased rates of adherence seen in the MI-FREEE trial are encouraging, it is important to evaluate the effect of systems to decrease cost-related non-adherence on primary prevention of cardiovascular events in patients with diabetes and dyslipidemia.

Medication Therapy-Related Factors

Factors related to medication therapy effect medication adherence rates. The complexity and dosing frequency of the treatment regimen is an important determinant of adherence to medication. Several studies have described the importance of dosing frequency on adherence [18, 19]. More recent data suggest the size of this effect. An analysis of pharmacy claims data for patients with atrial fibrillation and hypertension or diabetes found patients on daily dosing schedules had 26 % higher rates of adherence than those on twice daily dosing schedules [20]. These data support a significant contribution of dosing frequency to medication adherence in patients with diabetes mellitus and another chronic medical condition. Data comparing dosing schedules of multiple medications in patients with diabetes are needed to guide the development of medical regimens that minimize medication non-adherence while conferring adequate medical benefit.

Side effects limit the tolerability and safety of prescribed medication and therefore influence adherence. The impact of side effects of oral anti-hyperglycemics on adherence was

evaluated in the RECAP-DM study [21]. The study followed 1709 patients in Europe with diabetes mellitus who had failed metformin monotherapy and were started on either a sulfonylurea or thiazolidinedione as additional therapy. The study examined the relationship between the occurrence of hypoglycemia, patient satisfaction with treatment, patient-perceived barriers to adherence, and patient-reported medication adherence. Patients who experienced hypoglycemia were more likely to report barriers to treatment adherence. These patients rated the efficacy, convenience, and satisfaction with treatment significantly lower than patients who did not experience hypoglycemia. While there was no statistically significant difference in self-reported adherence rates between patients who did and those who did not experience hypoglycemia, 40.9 % of all patients who reported barriers to adherence cited medication side effects as the reason for non-adherence. These data suggest medication side effects are a significant risk factor for non-adherence to multiple medications. Work to establish a structured way to assess for and respond to side effects to medications is needed in order to improve medication adherence in patients with diabetes mellitus.

It is important to note that patient-perceived barriers to medication adherence are heterogeneous in a patient population. A survey of diabetic patients taking oral anti-hyperglycemic medications demonstrated different patient groups report varying barriers to medication adherence [22]. In this study, women were more likely than men to report concerns regarding medication-related weight gain as a barrier to medication adherence. In addition, as compared to patients with a college education, patients without a college education were more likely to cite concern regarding cardiovascular risk associated with oral anti-hyperglycemic as factor influencing medication adherence. These data support the relationship between side effects and medication adherence. In addition, they suggest this effect is heterogeneous within a given population. It is unclear what sub-groups of patients are more likely to have decreased adherence related to particular side effects. Further delineation of groups at risk for medication non-adherence related to particular side effects will allow for more directed interventions targeting individual patients at risk for non-adherence due to medication side effects.

Patient-Related Factors

Patient-related factors vary in their relative contributions to adherence to multiple medications. Low health literacy has been implicated as a potential barrier to adherence to medical therapy for patients with chronic medical conditions, though the data examining this hypothesis are conflicting. In addition, poor health literacy has been implicated as a mechanism to explain racial disparities in adherence to diabetes medications [23]. However, a recent review of data regarding the relationship between health literacy and adherence to medical therapy

for diabetes mellitus and cardiovascular disease described only one study demonstrating an association between health literacy and refill adherence [24]. In contrast, the recent DISTANCE trial examined the effects of low health literacy on adherence to anti-depressant medications in patients with diabetes [25]. The majority of patients in the trial (72 %) were classified as having health literacy limitations. As compared to patients without health literacy limitations, those with poor health literacy had significantly worse anti-depressant medication adherence as defined by several measures. While these data suggest a relationship between poor health literacy and medication adherence, the nature of this relationship remains unclear.

Increased alcohol use coincident with other chronic medical conditions is often associated with lower rates of medication adherence [26]. Among patients taking both statins and oral anti-hypertensives, increased rates of medication non-adherence have been associated with higher rates of alcohol use [27]. Depression is another coincident chronic condition associated with rates of medication adherence. Increased depressive symptoms have been associated with lower rates of medication adherence [28]. The mechanisms underlying this association remain unclear, though lack of social support is one of several factors implicated.

The severity and complexity of medical illness is associated with the level of adherence to medications. In a French study, patients with a history of acute coronary syndrome (ACS) who had severe non-cardiovascular disease were noted to have lower rates of adherence to medications for secondary prevention of coronary heart disease than patients without coincident severe non-cardiovascular disease [29]. A study of elderly Canadian patients with non-cardiovascular atherosclerotic disease were at higher risk for non-adherence to medications for coronary heart disease than those without non-cardiovascular atherosclerotic disease [30].

Patient beliefs and attitudes toward medication and illness influence adherence rates. Patients' perceived benefits of medications are positively and strongly associated with their intention to take diabetes medications [31]. However, the lack of accepted metrics to quantify patient beliefs limit insight into their effect on medication adherence. A recent analysis surveyed older adults taking multiple medications regarding their perceived benefits and risk of medications [32]. A low ratio of patient-reported perceived benefit to risk (indicating the patient perceived less benefit and more risk associated with their medication) was associated with lower rates of adherence. Another construct of patient beliefs, diabetes fatalism - a complex psychological condition characterized by feelings of despair and hopelessness - is associated with poor medication adherence [33]. The factors that influence patient perceptions and beliefs remain poorly understood. One recent survey of patients taking multiple medications found that seeking information regarding medications an autonomous source (i.e., not the prescribing physician) was associated with higher

rates of non-adherence [34]. As a whole, recent data regarding the effect of patient beliefs on medication adherence suggest a strong relationship. However, these factors are challenging to define. Designing metrics to evaluate changes in patient beliefs in response to an intervention aimed at improving medication adherence is challenging. A better understanding of the complex construct of patient perceptions regarding the relative benefit and risk of medication will inform further strategies to improve medication adherence.

Health Provider and Health System-Related Factors

Patient perceptions of the quality of communication with their health care provider also influences medication adherence. A recent study examined the relationship of communication between patient and provider and medication adherence in patients taking one or more oral anti-hyperglycemic, lipid-lowering, or antihypertensive medication [35]. Communication was measured with a four item Consumer Assessment of Healthcare Providers and Systems Survey (CAHPS) score, with a lower score reflecting lower patient-perceived quality of communication. In this analysis, CAHPS score was related to medication adherence, with every 10-point decrease corresponding to an increase in adjusted prevalence of poor adherence of 0.9 %. The association between quality of communication and adherence was larger for oral anti-hyperglycemic medications than for other medications. This study highlights the importance of patient perceptions of the quality of communication with their health care providers and medication adherence.

Ways to Improve Non-Adherence

Interventions designed to improve adherence may target individual patients, health care providers, or the health system (Table 2). These strategies address the mechanisms underlying non-adherence to multiple medications. Many approaches simultaneously address multiple challenges to medication adherence.

Patient-Targeted Approaches

Strategies to address therapy-related barriers to medication adherence in patients with diabetes and dyslipidemia have

Table 2 Ways to improve medication adherence in patients taking multiple medications

Patient-targeted	Fixed-dose prescribing ("polypill")
Health care provider-targeted	Multidisciplinary care team Regular contact with care team
Health system-targeted	Elimination of medication co-payment Value-based insurance program

primarily focused on reducing the complexity of the prescribed medical regimen. As has been discussed, polypharmacy is a potentially modifiable and important component of adherence to medical therapy for patients with chronic conditions. Fixed-dose prescribing (also referred to as the “polypill”) as a strategy to improve medication adherence in patients with diabetes has been evaluated in several studies. An early, large-scale study of pharmacy claims data aimed to assess changes in medication adherence associated with fixed-dose combination pills as compared to loose-pill combinations in patients with type 2 diabetes mellitus [36]. The authors compared the rates of adherence of 16,928 patients whose diabetes was poorly controlled on either metformin or thiazolidinedione mono-therapy and were subsequently transitioned to rosiglitazone-metformin therapy either as a fixed-dose combination pill or as a loose-pill combination. Rates of adherence were significantly improved in patients transitioned to fixed-dose combination therapy as compared to those taking loose-pill combination therapy.

The beneficial role for fixed-dose combination treatment as a strategy to improve medication adherence in patients with type 2 diabetes is supported by a recent meta-analysis. The analysis included seven trials that reported data on the effect of fixed-dose therapy on medication adherence. Adherence was 10–13 % higher for fixed-dose therapy than for loose-pill therapy for patients starting combination therapy [37]. For patients already taking loose-pill combination therapy, switching to fixed-dose therapy increased adherence 3.5 %–12.4 %, while for those remaining on loose-pill therapy changed adherence -1.5 %–5 %. These data suggest a role for fixed-dose combination therapy as a strategy improve medication adherence in patients with type 2 diabetes mellitus. To date, however, there are no available randomized-control trials evaluating the effect of fixed-dose therapy with oral anti-hyperglycemics and therapies for dyslipidemia on medication adherence or macrovascular outcomes.

Health Care Provider Approaches

Many groups of health care providers care for patients with diabetes and dyslipidemia. Strategies aimed at improving medication adherence have increasingly focused on the role of the multidisciplinary care team. A team-based approach to the chronic care model for the management of patients with coincident diabetes, obesity, and hypertension has been associated with improvement in HgbA1c, body mass index (BMI), and systolic blood pressure when compared to a traditional chronic care model [38]. A number of strategies have been employed in an attempt to adopt a multidisciplinary approach to the management of diabetes and dyslipidemia. A recent study examined the effect of nurse-led counseling regarding cardiovascular risk on adherence to statins [39]. Patients taking statins for either primary or secondary prevention of cardiovascular disease were randomized to routine care or to an

intervention arm. The intervention consisted of nurse-led individualized counseling regarding cardiovascular risk and subsequent regular visits to assess the degree of control of dyslipidemia and other cardiovascular risk factors. At the completion of the trial, self-reported adherence to statins was significantly higher in the intervention arm as compared to those who received routine care (95 %–100 % versus 90 %–95 %, respectively, $p < 0.05$). The effect of nurse-led risk factor counseling on adherence to statins in patients with diabetes remains unclear. However, this study provides an important model for increasing adherence to medication therapy for dyslipidemia and suggests a role for regular nurse-led counseling regarding cardiovascular risk in the care of patients with diabetes and dyslipidemia.

The importance of regular contact with members of the health-care team on rates of medication adherence has been noted in other interventions. The potential role of a pharmacist-led management model for patients with diabetes was examined in a recent trial [40]. Patients were randomized to usual care or to an intervention arm consisting of an initial face-to-face meeting with a pharmacist and subsequent 8 weekly telephone calls from a pharmacist to patients. Self-reported medication non-adherence was significantly lower in the intervention as compared to the usual care group. Of patients 28.6 % in the intervention group reported medication non-adherence, as compared to 64.6 % of patients in the usual care group ($p = 0.003$). These data support the efficacy of a team-based care model to increase medication adherence for patients with diabetes and coincident chronic conditions such as dyslipidemia. It is important to note not all studies examining the role of a multidisciplinary care team approach have demonstrated a positive effect on medication adherence. In a study of patients from 14 primary care sites with poorly controlled diabetes mellitus or coronary heart disease, patients randomized to an intervention of a nurse care manager collaborating closely with primary care physicians, consultants, and patients did not have an increase in medication adherence as compared to patients randomized to usual care [41]. While the majority of data support the benefit on medication adherence of a multidisciplinary care model over a traditional care model, the optimal strategy remains unclear. Data are lacking regarding the relative efficacy of different available models. Further, it remains unknown how best to target specific care models to particular patient populations in order to improve adherence in a panel of patients with a variety of barriers to medication adherence.

Health System Approaches

Health system approaches to improving medication adherence address barriers related to access to care and delivery of care. Strategies that decrease the cost of medications for patients are associated with increased medication adherence. The previously discussed MI-FREEE trial [16] randomized patients

post-MI to usual prescription coverage or full prescription coverage for medications for secondary prevention of coronary heart disease. Adherence rates to the covered medications were significantly higher in the full prescription coverage group as compared to the usual coverage group. The effectiveness of this strategy in patients with diabetes was evaluated in a recent study. A prospective cohort study evaluated the effect of a value-based insurance design on patient-centered outcomes including medication adherence in patients with diabetes mellitus [42]. The value-based insurance program eliminated co-payments for diabetes-related medications and supplies for patients of a large health care system and their dependents with diabetes for one year. As compared to prior to initiation of the value-based insurance program, cost-related non-adherence decreased significantly. In addition, patient-reported medication adherence for oral anti-hyperglycemic medications increased significantly with the program. The institution of health system changes may allow for reduction in social and economic-related, as well as health care access-related, barriers to adherence. The additional benefit of strategies aimed at addressing patient-, therapy-, and provider-related barriers is unknown.

Conclusions

Medication non-adherence is a significant issue for patients with multiple medical conditions, such as diabetes and dyslipidemia. Understanding factors associated with non-adherence can inform efforts to improve it. Increased rates of medication adherence lower the long-term consequences of chronic disease including atherosclerosis in patients with diabetes.

Patients with diabetes mellitus and dyslipidemia face many barriers to medication adherence that can be grouped into patient-, social and economic-, therapy-, and health provider and health-system related factors. Recent data support that sub-optimal medication adherence and poor health literacy contribute to racial disparities in outcomes for patients with diabetes. Cost-related medication non-adherence has recently been described as a significant and frequent barrier to adherence. The magnitude of the beneficial effect of a once daily dosing schedule was suggested in a recent analysis in which patients prescribed a once daily medication reported adherence rates 26 % higher than those for patients prescribed twice daily dosing schedules. Patient perceptions regarding the benefits and risks of the medication regimen, as well as patient beliefs regarding illness, have recently been associated with medication adherence. It remains unclear how patient perceptions influence adherence, though the construct of “diabetes fatalism,” as well as the association between seeking information from an autonomous source and non-adherence, may help explain this relationship. The quality of communication between patient and health provider may further influence the adherence rates.

Recent efforts aimed at improving medication adherence in patients with diabetes have addressed systems of health care delivery and cost-related barriers to adherence. Nurse or pharmacist-led management programs have recently been shown to increase rates of medication adherence as compared to traditional care models. In addition to the earlier MI-FREEE trial, the recent success of a value-based insurance program (in which co-payments for diabetes medications are eliminated) in increasing medication adherence rates supports the role for health-system level strategies to decrease cost-related non-adherence. Future programs designed to improve medication adherence should focus on mechanisms to identify, and then intervene upon, barriers faced by individual patients. Current data regarding risk factors for medication non-adherence should inform screening programs within populations of patients. Health system approaches to improve medication adherence for patients with diabetes and dyslipidemia should focus on the organization of multifaceted management teams. More data is needed to understand how these teams can better identify barriers faced by individual patients and apply resources available to improve medication adherence.

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Compliance with Ethics Guidelines

Conflict of Interest Lucas N. Marzec and Thomas M. Maddox declare that they have no conflict of interest.

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