ORIGINAL RESEARCH

Adherence to Statin Therapy and Attainment of LDL Cholesterol Goal Among Patients with Type 2 Diabetes and Dyslipidemia

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Background: Statins are widely utilized antidyslipidemics with a proven track record of safety and efficacy. However, the efficacy of these therapeutic agents hinges on patients' adherence to their prescribed statins.

Objective: The primary objectives of this study were to examine the relationship between adherence to prescribed statins and its impact on the low-density lipoprotein (LDL) level, and to explore the factors that influence patient adherence to statins among patients with diabetes and dyslipidemia.

Methods: This was a retrospective, cross-sectional study using the electronic health records data of adults (≥18 years) with type 2 diabetes and dyslipidemia visiting outpatient clinics at a university-affiliated tertiary care center. Adherence to statin therapy was estimated using the proportion of days covered (PDC). Patients with diabetes were considered adherent to statins if they had a PDC of ≥80%. Treatment success was considered if the LDL level of < 2.6 mmol/L.

Results: Out of 10,226 of patients with diabetes, 1532 met the inclusion criteria and were included in the study. Seventy-nine percent of the patients with diabetes were on atorvastatin and 21% were on simvastatin. The vast majority of the patients with diabetes (77%) were considered adherent and about 42% achieved LDL-cholesterol goal < 2.6 mmol/L. No association between adherence to statin therapy and LDL goal attainment was observed. Women had lower odds of being adherent to statin therapy (AOR=0.66, 95% CI: 0.49–0.87) compared to men. Further, young adults (18–44 years) had lower odds of being adherent to statin therapy (AOR=0.58, 95% CI: 0.32–0.97) compared to older adults (age>65 years).

Conclusion: The findings of this study highlight the need to examine the impact of adherence to statins on healthcare services utilization due to different complications of uncontrolled dyslipidemia.

Keywords: statins, adherence, dyslipidemia, diabetes, low-density lipoprotein cholesterol

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Introduction

Dyslipidemia is a prevalent disorder affecting more than one-third of the adult population (≥18 years) in Saudi Arabia[1–3] putting them at higher risk of coronary heart disease (CHD) and mortality.[4] Therefore, the National Cholesterol Education Program (NCEP-III) urges health care specialists to start on intensive low-density lipoprotein (LDL) cholesterol reducing program for patients with CHD.[5] Moreover, the NCEP-III guidelines emphasize the importance of managing dyslipidemia among patients with diabetes since they have a similar risk of experiencing CHD

events as patients with an established history of CHD. The target LDL level for patients with diabetes is < 2.6 mmol/L (100mg/dL) according to both the NCEP-III and the American Diabetes Association guidelines.[6]

The mainstay of dyslipidemia treatment was and still orally administered antidyslipidemic agents. However, there are multiple classes within this therapeutic group, such as statins which earned top-tier status in the management of dyslipidemia given their proven track record of efficacy and safety compared to other antidyslipidemics. Therefore, it is ranked by the NCEP-III as the first-line treatment for dyslipidemia.[5] Furthermore, statins are recommended for primary prevention of CHD among adults by the American Heart Association (AHA) guidelines.[7] This recommendation by the AHA was largely based on generated evidence from multiple randomized clinical trials suggesting a significant reduction in the risk of cardiovascular disease and stroke morbidity and mortality following statin therapy.[8–10] Thus, intensive treatment of dyslipidemia using statins among high-risk patients such as those with diabetes is warranted.

The clinical effectiveness of statin therapy is contingent upon its ability to significantly reduce the LDL cholesterol level, and failure to reach that goal due to lack of follow-up, inadequate coordination of care, or poor adherence to statin therapy may render these therapeutic agents ineffective.[11] Therefore, adherence to statin therapy, which was defined as the extent to which patients take their prescribed medication regimens as instructed by their healthcare providers cannot be overemphasized.[12] Poor adherence to statin therapy can be attributable to multiple reasons such as intolerable side effects,[13] asymptomatic nature of the disease (e.g. dyslipidemia), high number of medications,[14–17] socioeconomic status (e.g., age, gender),[18,19] coexisting chronic health conditions,[16,17,19] complex treatment regimen, poor patient-provider communication,[20] and financial constraints.[20] Hence, ensuring optimal adherence to statin therapy is often challenging as dyslipidemia is an asymptomatic chronic illness and patients sometimes do not recognize the importance of adherence to their statin therapy. This was confirmed in multiple studies. For example, in a prospective cohort study that was conducted among elderly patients taking statins to assess their level of adherence to statin therapy found that only 26% of the patients with diabetes were adherent to their prescribed statin.[21] Another study estimated that approximately 50% of the patients on statins continued their therapy at six months and only 30–40% at one year.[22]

Adherence to statin therapy is critical to the primary prevention of cardiovascular disease.[23] Several studies have demonstrated a positive relationship between adherence to statin therapy and LDL goal attainment.[11,24,25] In a retrospective analysis of 21,239 new statin therapy users, patients who were adherent to their prescribed statins in the first 90 days of statin therapy initiation were more likely to reach their therapeutic goal in lowering the LDL cholesterol levels.[24] Moreover, another study has investigated the relationship between adherence to statin therapy and lower LDL cholesterol levels among a sample of 653 patients treated for dyslipidemia and found that adherence to statin therapy was significantly higher among patients with a controlled level of LDL.[11] Similarly, in another retrospective cohort study among 1607 patients using a large employer-based health insurance plan claims data, LDL levels were significantly lower among patients with a Medication Possession Ratio (MPR) of ≥80, which is indicative of adequate adherence, compared to their counterparts with an MPR of <80%.[25]

Studies that have evaluated patient adherence to statin therapy among patients with diabetes are limited.[11] Identifying the root causes of poor adherence to statin therapy is important to help identify gaps in the quality of provided healthcare, which can be instrumental in designing individualized interventions aimed at improving adherence to this vital cost-effective class of medications. Therefore, the objective of this study was to examine the association between adherence to statin therapy and LDL cholesterol goal attainment. Further, factors that affect adherence to statin therapy in patients with type 2 diabetes and dyslipidemia were identified.

Methods
Study Design
A retrospective, cross-sectional, electronic health records (EHRs) review study was conducted in a university-affiliated tertiary hospital in Riyadh, Saudi Arabia. The hospital is one of the largest teaching hospitals in Riyadh, which serves as a referral center for patients primarily from the northern region of Saudi Arabia as well as other regions.

Data Source and Data Extraction
Data were extracted from the EHRs database for a 12-month period (1st January 2017 to 30th December 2017). The data that were derived from the EHRs include demographics (e.g., age, gender, nationality), clinical data (e.g., LDL

cholesterol), and clinical diagnosis, which was reported using the clinical diagnosis codes (Appendix I), and prescription drug information (e.g., drug name, dispensing date, quantity dispensed, days of supply and refills).

Ethics Approval and Consent to Participate

The study was approved by the institutional review board of King Saud University Medical City (IRB# E-18-3401) and all participants provided informed consent. Patients' identification numbers were encrypted to maintain the confidentiality of the data and stored in password protected and limited accessed computers.

Study Population

Adults aged ≥18 years, diagnosed with dyslipidemia and type 2 diabetes (using the ICD-10-CM clinical diagnoses codes) from the outpatient setting during a one-year period were included in the study. This study has included only patients who received at least two prescription fills of statin therapy to enable us to calculate the PDC. Patients with missing laboratory observations for LDL cholesterol levels as well as those whose latest LDL cholesterol measurement was within 30 days after the first statin therapy prescription or LDL cholesterol measurement before statin therapy in the EHRs database were excluded.

Measures

Dependent Variable: Adherence to Statin Therapy

The proportion of days covered (PDC) was used to measure adherence to statin therapy. Several studies have reported adherence using the PDC measure based on EHRs data and administrative claims data.[11,17,18,26] PDC was calculated as total days of supply divided by days in the follow-up period (PDC = (total days supply/total number of days evaluated) × 100%). The date of the first filled statin prescription was considered as the index date. The total days supplied for statin therapy were calculated from the index date till the end of 2017. Patients were considered adherent to statin therapy regimen if their estimated PDC was ≥80%.[26] Only two statin therapies were identified in this study (i.e., simvastatin, atorvastatin) as they are the only approved formulary medications.

Main Independent Variable: LDL Cholesterol Goal Attainment

The main independent variable was LDL cholesterol goal attainment which was defined as an LDL level below 2.6

mmol/L (<100mg/dl) based on the NCEP-III recommendation for patients with diabetes.[27] This threshold has been reported in the literature to identify LDL cholesterol goal attainment among patients with type 2 diabetes and dyslipidemia.[11]

Other Independent Variables

Demographics (e.g., age, sex), marital status, chronic health conditions, and polypharmacy were included in the study. Chronic health conditions included hypertension, asthma, osteoarthritis, osteoporosis, anxiety, and depression. These conditions were highly prevalent among patients with type 2 diabetes and dyslipidemia. Polypharmacy was defined as the use of five or more medications (≥5 medications). This definition is the most utilized definition of polypharmacy since there is not a consensus on its definition.[28–30]

Statistical Analysis

Frequencies and percentages were used to describe the categorical variables (gender, marital status, nationality, co-existing chronic conditions, and polypharmacy). Means and standard deviations were used to describe continuous variables (age, adherence, LDL Cholesterol level). Chi-square and Fisher's exact tests were used to examine the factors related to adherence to statin therapy. Multiple regression analysis was conducted to examine the relationship between LDL cholesterol level and adherence to statin therapy controlling for age, sex, marital status, nationality, hypertension, asthma, osteoarthritis, osteoporosis, anxiety, depression, and polypharmacy. All statistical analyses were performed using the Statistical analysis software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Description of the Study Population

The number of patients who met the inclusion criteria and were included in the study was 1532. Table 1 displays the characteristics of the study population. The majorities of the study population were women (71%) and aged 45 to 64 years (68%). Hypertension was the most prevalent comorbid health condition among the study sample (68.6%). Approximately 73% of the patients with diabetes had polypharmacy (≥5 medications).

Adherence to Statin Therapy and LDL Cholesterol Goal Attainment

Overall, 77.4% of the patients with type 2 diabetes and dyslipidemia had adequate adherence to statin therapy and

Table 1 Characteristics of the Study Population Number and Row Percentage of Characteristics by Statin Adherence Among People with Type 2 Diabetes and Dyslipidemia

	Total		Adequate Adherence PDC ≥0.8		Poor Adherence PDC<0.8		P-value	Sig.
	N	%	N	%	N	%	Chi-Square Value	
	1532	100.0	1186	77.4	346	22.6			
Age Mean (SD)	58.8 (10)		58.9(10)		58.0(10)			
LDL Mean (SD)	2.6 (0.89)		2.5(0.8)		2.6(0.9)			
Age Group							3.81	0.28
18–44	106	6.9	77	72.6	29	27.4		
45–54	397	25.9	298	75.1	99	24.9		
55–64	646	42.2	510	78.9	136	21.1		
≤65	383	25.0	301	78.6	82	21.4		
Gender							14.29	0.00	***
Men	443	28.9	371	83.7	72	16.3		
Women	1089	71.1	815	74.8	274	25.2		
Marital Status							2.80	0.09
Single	107	7.6	90	84.1	17	15.9		
Married	1297	92.4	1000	77.1	297	22.9		
Nationality							1.59	0.21
Saudi	1397	91.4	1076	77	321	23		
Non-Saudi	132	8.6	108	81.8	24	18.2		
Hypertension							0.70	0.40
Yes	1051	68.6	820	78	231	22		
No	481	31.4	366	76.1	115	23.9		
Asthma							0.65	0.42
Yes	134	8.7	100	74.6	34	25.4		
No	1398	91.3	1086	77.7	312	22.3		
Osteoarthritis							0.32	0.57
Yes	109	7.1	82	75.2	27	24.8		
No	1423	92.9	1104	77.6	319	22.4		
Osteoporosis							0.04	0.84
Yes	65	4.2	51	78.5	14	21.5		
No	1467	95.8	1135	77.4	332	22.6		
Anxiety							3.15	0.08
Yes	63	4.1	43	68.3	20	31.7		
No	1469	95.9	1143	77.8	326	22.2		
Depression							3.98	0.05	*
Yes	29	1.9	18	62.1	11	37.9		
No	1503	98.1	1168	77.7	335	22.3		
Polypharmacy							6.08	0.02	*
≥5	1116	72.8	846	75.8	270	24.2		
0 to 4 drugs	416	27.2	340	81.7	76	18.3		
LDL goal attainment							0.002	0.964
<100	636	41.5	492	77.4	144	22.6		
≥ 100	896	58.5	694	77.5	202	22.5		

Notes: Study population comprised of 1532 People with type 2 diabetes and dyslipidemia (age ≥18year) who visited outpatient's clinics from a tertiary hospital. Polypharmacy was defined as the use of five or more medications. Asterisks (*) represent significant differences in statin adherence from chi-square tests and Fisher's exact tests. ***P< 0.001; *0.01 ≤ p < 0.05
Abbreviations: LDL, low density lipoprotein level; PDC, Proportion of Days Covered; SD, Standard Deviation; Sig, Significance.

41.5% of them achieved the LDL cholesterol goal of < 2.6 mmol/L (Table 1). The most frequently prescribed statin therapy was atorvastatin (79.2%) followed by simvastatin (20.8%) (Table 2). The mean LDL cholesterol level was 2.61 mmol/L. The majority of patients with diabetes (77.4%) who attained LDL cholesterol target had adequate adherence (PDC ≥80%) to statin therapy.

Factors Associated with Adherence to Statin Therapy

Table 1 also displays the unadjusted associations between independent variables and adherence to statin therapy. No significant association between adherence to statin therapy and LDL cholesterol goal attainment was found, however, adherence to statin therapy significantly differed by gender, depression, and polypharmacy. A significantly higher percentage of patients with diabetes with adequate adherence (PDC ≥80%) to statin therapy was observed among men compared to women (83.7% vs 74.8%, P value = 0.0001). Further, the percentage of patients who were adherent to statin therapy was significantly higher among patients without polypharmacy compared to those with polypharmacy (81.7% vs.75.8%, P-value = 0.02).

Adjusted odds ratios (AORs) and 95% confidence intervals (CI) from the multivariable regression analysis on statin adherence are presented in Table 3. Among patients with type 2 diabetes and dyslipidemia, there was an association between adherence to statin therapy and LDL goal attainment. Those who attained LDL cholesterol target did not have higher odds of being adherent to statin therapy compared to those who did not attain LDL cholesterol target (AOR=1.27, 95% CI: 0.97–1.66). Women had lower odds of being adherent to statin therapy (AOR=0.66, 95% CI: 0.49–0.87) compared to men. Also, young and middle-aged adults (18–44 years) had lower odds of being adherent to statin therapy (AOR=0.58, 95% CI: 0.32–0.97) compared to other age groups (≥45 years). Furthermore, those with polypharmacy use had lower odds

of being adherent to statin therapy compared to those without (AOR= 0.67, 95% CI: 0.47–0.96).

Discussion

The study estimated the adherence rate to statin therapy among patients with type 2 diabetes and dyslipidemia and identified factors associated with adherence to statin therapy. Around two-thirds of the study population had adequate adherence to statin therapy, which is consistent with the 73% adherence rate published by Parris et al who also assessed the adherence rate in patients with diabetes and dyslipidemia.[11] The reported adherence rates in this study are also within the adherence range to statin therapy reported in other studies (68–80%).[25,31]

Regarding the main independent study variable, 42% of the study population attained the LDL cholesterol goal.[5] This finding is consistent with some of the published studies.[11,25] Parris et al reported that 44% of adults with diabetes and dyslipidemia achieved their LDL cholesterol goal,[11] while Wayne et al reported that only 30% of the patients achieved optimal LDL cholesterol goal.[25] After adjusting for confounding factors, no association between adherence to statin therapy and LDL cholesterol goal attainment was observed in this study. Published studies have reported that patients who attained LDL cholesterol goal had a higher adherence rate to the statin therapy than those who did not.[11,25] Another published study has reported no association between adherence to statin therapy and LDL cholesterol goal attainment.[19] Interestingly, despite the high adherence rate to statin therapy, the level of LDL-C target achievement was low among the study sample. This could be attributable to unmeasured factors such as patients' physical activity and dietary patterns. Unfortunately, these factors were not captured in this study. There is evidence to suggest that nonadherence to statins results in negative health consequences such as higher LDL cholesterol, risk of cardiovascular mortality, hospitalizations, and higher healthcare costs.[32]

Table 2 Statin Therapy, Adherence to Statin Therapy and LDL Cholesterol Goal Attainment

Statin	N (%)	Mean LDL (mmol/L)	% Attain LDL goal	Mean PDC (Min, Max)	% Adherent to Statin PDC
All statin	1532 (100.0%)	2.61	41.51	0.88 (0.37–1.0)	77.42
Atorvastatin	1213 (79.2%)	2.60	67.50	0.88 (0.37–1.0)	76.40
Simvastatin	319 (20.8%)	2.64	67.70	0.89 (0.45–1.0)	81.20

Note: Mean PDC range from 0 to 1.
Abbreviations: LDL, low density lipoprotein level; PDC, Proportion of Days Covered.

Table 3 Adjusted Odds Ratios and 95% Confidence Intervals from Logistic Regression on Adherence to Statin Therapy People with Type 2 Diabetes and Dyslipidemia

	AOR	95% CI	P value	Sig.
Age Group				***
18–44	0.56	[0.32, 0.97]	0.027	
45–54	0.73	[0.49, 1.07]	0.083	
55–64	0.93	[0.66, 1.32]	0.636	
>65 (Ref.)				
Gender				**
Women	0.64	[0.47, 0.87]	0.003	
Men (Ref.)				
Marital Status				
Single	0.56	[0.32, 0.98]	0.051	
Married (Ref.)				
Nationality				
Non-Saudi	0.78	[0.48, 1.28]	0.308	
Saudi (Ref.)				
Hypertension				
Yes	1.20	[0.89, 1.62]	0.138	
No (Ref.)				
Asthma				
Yes	0.95	[0.60, 1.49]	0.892	
No (Ref.)				
Osteoarthritis				
Yes	0.78	[0.48, 1.27]	0.307	
No (Ref.)				
Osteoporosis				
Yes	1.15	[0.58, 2.26]	0.719	
No (Ref.)				
Anxiety				
Yes	0.60	[0.33, 1.08]	0.114	
No (Ref.)				
Depression				
Yes	0.54	[0.23, 1.24]	0.155	
No (Ref.)				
Polypharmacy				*
≥5	0.67	[0.47, 0.96]	0.011	
0 to 4 drugs				
LDL goal attainment				
Yes	1.27	[0.97, 1.66]	0.726	
No				

Notes: *Study Population Comprised of 1532 People with type 2 diabetes and dyslipidemia who Visited Outpatient's Clinics from Tertiary Hospital. Asterisks (*) represent significant differences based on statin adherence from logistic regressions with poor adherence as the reference group. ***P< 0.001; **0.001 ≤ p < 0.01; *0.01 ≤ p < 0.05.
Abbreviations: AOR, Adjusted Odds Ratio; CI, Confidence Interval; Ref, Reference group; Sig, significance.

In this study, men had a significantly higher adherence rate to statin therapy compared to women, which is consistent with other published studies.[11,18,19,33] Further, young and middle-aged adults had higher adherence rate to statin therapy compared to older age groups something that was noted in previously published studies.[18] Polypharmacy was also identified as one of the obstacles to adherence to statin therapy. In fact, patients with diabetes are reported to be at a higher risk of being on multiple prescription medications mainly due to diabetes and other comorbid health conditions and at higher risk of drug-drug interaction as compared to non-diabetic counterpart.[34,35] Polypharmacy among patients with Type II diabetes has been linked to many negative health consequences such as higher risk of all-cause mortality and myocardial infarction as reported by a recent systematic review and meta-analysis study.[36] Several studies have shown a significant relationship between polypharmacy and poor adherence to statin therapy.[14,15] Simplifying medication regimens by pharmacists and other healthcare providers should have a positive impact on different health outcomes among patients at high risk of cardiovascular disease such as patients with diabetes and dyslipidemia.

It is important to tackle and manage dyslipidemia in patients with diabetes. Dyslipidemia, as part of the metabolic syndrome, is a cardio metabolic risk factor not only for CHD, but also for other heart diseases, such as atrial fibrillation.[37] Besides, the use of statins in patients with diabetes can aid in reducing inflammation and oxidative stress levels which also contribute to the pathogenesis of other cardiovascular risk factors such as obesity, diabetes, CHD.[38–40]

Multiple practical implications can emanate from the present study findings. Adherence to medications depends on the availability of patient counseling and medication therapy management especially among patients with low health literacy level. Therefore, improving the quality of pharmaceutical care is essential to achieve an optimal level of adherence to prescribed drug regimens especially among patients with diabetes. Moreover, public health campaigns to raise public awareness of the importance of adherence to essential medications such as antidyslipidemic agents. In addition, a multidisciplinary policy approach aimed at patients with diabetes, healthcare providers, and healthcare systems should be designed to manage dyslipidemia effectively and prevent major complications. Such policies should entail simplifying treatment regimens, reinforcing and rewarding adherence, encouraging healthcare providers to adhere to treatment

guidelines, and providing lipid management clinic services.[5] The study findings suggest that endocrinologists and primary care healthcare providers need to provide routine screening for LDL level, especially for young adults, women, and those who are taking multiple medications. These screenings can detect LDL goal attainment and thus help in improving adherence to statin therapy, thereby preventing the exacerbation of the disease condition and the subsequent negative health consequences. As competing demands to treat multiple conditions may impede the management of LDL cholesterol level, endocrinologists and primary care healthcare providers may need to recognize the non-adherence issue early thereby impacting positive patient outcomes. These should help in the early detection and management of high LDL cholesterol levels as well as in improving adherence to prescribed drug regimens including statins.

Although this study is one of few studies that examined the association between adherence to statin therapy among patients with diabetes and dyslipidemia and LDL cholesterol goal attainment, it has some limitations. The fact that this was a single center study limits the generalizability of its findings. Moreover, the study used the PDC which is a valid and widely used proxy measure for medication adherence, however, it is hard to accurately determine medication adherence using this measure alone since some patients may unintentionally forget or refuse to take their medications due to side effects or other personal reasons. In addition, the causality between adherence to statin therapy and LDL cholesterol goal achievement cannot be established based on the current study design. Finally, multiple covariates have been controlled for in the study; however, some unmeasured confounders such as social factors and patients' beliefs which cannot be captured using EHRs were not controlled for.

Conclusions

The findings of this study highlight the need to develop different strategies aimed at improving adherence to life-saving medications such as statins. Future studies should evaluate the impact of long term adherence to statin therapy on the incidence rate cardiovascular diseases and other major complications, healthcare services utilization and costs, and health-related quality of life among patients with diabetes and dyslipidemia.

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Disclosure

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