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Review Article

Prevalence of Adherence to Anti-hyperlipidemia Medication Among Adults in the Gulf Cooperation Council: A Narrative Scoping Review

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Abstract

Introduction: Hyperlipidemia, a silent asymptomatic disease, contributes significantly to cardiovascular disease (CVD) mortality and morbidity in the Gulf Cooperation Council (GCC) region. One of the facets of preventing CVD endpoint is medication adherence to lipid-lowering drugs (LLDs). Accordingly, this scoping review aims to explore the adherence to anti-hyperlipidemia medications among adults in the Arabian Gulf region.

Methods: Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a literature search was conducted in Scopus, PubMed, Web of Science, and Google Scholar to screen for articles published from 2013 to 2023 reporting adherence or compliance to LLDs among adults aged 18 years or above with or without any co-morbidities in the GCC region. The quality of the paper was assessed using the AXIS checklist.

Discussion: The search yielded 139 articles, six meeting our inclusion criteria, all of which were cross-sectional. The researchers utilized varied measuring tools, resulting in heterogeneous results: good adherence in two studies, low adherence in three, and indefinite results in one. Younger age, polypharmacy, and female gender were the variables associated with higher drug noncompliance in one or more studies.

Conclusion: There is a research gap on anti-hyperlipidemia medication adherence in the Arabian Gulf region which calls for further research, especially higher evidence studies as no attempts have been made beyond the cross-sectional design. Public health implications of the results may include awareness interventions and clinician-driven strategies to improve patient compliance.

Keywords: hyperlipidemia, dyslipidemia, adherence, Arabian Gulf, public health

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1. Introduction

Any abnormality in the levels of lipids such as cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride is known as dyslipidemia [1]. A rise in lipid levels like fats, cholesterol, and triglycerides in the blood is called hyperlipidemia. The normal range of various lipids is <5.2mmol/L for total cholesterol, <3.4mmol/L for LDL or 'bad cholesterol', and >1.0 mmol/L for HDL or 'healthy cholesterol'. Elevated lipid levels do not cause any symptoms, but they can lead to atherosclerosis or hardening of arteries, especially when LDL levels are high, which often comes under the term hypercholesterolemia [2]. Atherosclerotic obstructive lesions occurring in the coronary arteries lead to myocardial infarction whereas the same process in the arteries to the brain can be a common cause of stroke.

High cholesterol can be due to genetic conditions like in the cases of familial hypercholesterolemia or nongenetic conditions such as fatty diet, low physical activity, and other co-morbidities like diabetes and obesity. Therefore, with increased physical activity, diet changes, and weight loss, anti-cholesterol medications are usually prescribed to treat this chronic condition. Commonly used treatment is oral statin medications, followed by protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors injections when the former does not work or gives side effects [2].

Globally, high LDL cholesterol caused 4.4 million deaths in 2019, a 46.7% rise since 1990 [3]. Elevated cholesterol is responsible for one-third of ischemic heart disease cases and causes around 2.6 million deaths as well as 29.7 million disability-adjusted life years [4]. Specifically, in the Middle East and North African (MENA) region, ischemic heart disease or coronary artery disease (CAD) is the leading cause of mortality, morbidity, and disability with around 800,000 deaths in 2019 [5]. Within the Gulf Cooperation Council (GCC) region, one of the leading factors for coronary disease is dyslipidemia which is highly prevalent in the area [6].

Lower odds of cardiovascular disease (CVD) morbidity and mortality are associated with adherence and persistence to statin therapy as per a systematic review [7]. Yet, the World Health Organization reports that 50% of patients in developed countries are not adherent to chronic disease medications [8], with primary medication nonadherence is highest in hyperlipidemia [9]. In Middle Eastern studies, the level of adherence ranges from 1.4% to 88% [10]. Individual studies from GCC countries report high rates of decreased or suboptimal adherence among patients with chronic diseases [11–13]. However, evolocumab, a type of PCSK9 inhibitor, demonstrated high persistence levels in a sample of Saudi and Kuwaiti along with effectiveness and safety [14]. However, there is a gap in literature across the GCC region regarding studies focusing on adherence, predominantly among hyperlipidemia patients with no scoping reviews, systematic reviews, or randomized controlled trials conducted as per our search.

2. Methods

This scoping review aims to gather data on the studies reporting adherence or compliance to anti-hyperlipidemic to provide a foundation for further research, guide policies, improve adherence, and curb the CVD crisis in the region. Precisely, the primary objective of this scoping review is to estimate the level of adherence or compliance to anti-hyperlipidemia medications among adults in the GCC region. The secondary objective is to explore the factors associated with lower or higher adherence among the patients. An extensive search of the literature was carried out to answer the main aim of this scoping review with the following inclusion criteria:

1) Studies on adults aged 18 years or above with hyperlipidemia/dyslipidemia/hypercholesterolemia where their adherence/compliance to lipid-lowering drugs (LLDs) was measured
2) Studies conducted anywhere in the GCC region: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, or the United Arab Emirates (UAE)
3) Studies restricted from the year 2013 to 2023
4) Patients with co-morbidities like Type-2 diabetes mellitus, hypertension, or coronary episodes
5) Study design equal to or above the cross-sectional method in the hierarchy of evidence.

Meanwhile, the exclusion criteria were:

1) Studies including children under the age of 18 years
2) Studies with special populations like those with conditions related to oncology, obstetrics, and psychiatry
3) Grey literature.

The outcome measure of interest was adherence or compliance to anti-hyperlipidemia medication which is defined as “the extent to which the patient follows medical instructions” [8]. In literature, the most common methods used to measure adherence are questionnaire scales, pill counts, medication possession ratios, and pharmacy records [15].

Information was sourced from three databases (PubMed, Scopus, and Web of Science) along with one search engine (Google Scholar) to address any gaps in the search of this research niche. The time period covered for the results was from 2013 to 2023 whereas the time frame of the search was from October 16, 2023 to January 16, 2024.

The search string was formulated with a librarian in PubMed by searching medical subject headings (MeSH) terms related to high cholesterol and medication adherence. Thirteen keywords of the term ‘high

cholesterol' and 27 keywords of the term 'medication adherence' were created. Since PubMed did not produce MeSH terms for GCC, 16 keywords were created, independently. All of these MeSH keywords were then copied to a Word file and used for Scopus, Web of Science, and Google Scholar searches.

A total of 127 articles were produced from the database search with 68 articles from Scopus, 27 from PubMed, and 32 from Web of Science. Besides, 12 articles were selected from Google Scholar. Among these 139 articles, 30 sets of duplicates (3 duplicates each for 18 articles and 2 duplicates each for 12 articles) were found and 48 duplicate articles were deleted in total. Out of the remaining 91 studies, 57 articles were excluded after screening for abstracts and titles since they did not meet the inclusion criteria. Thus, 34 articles were assessed for eligibility and a full-text version was sought for retrieval. After an in-depth review, six articles were selected, and the remaining 28 articles were excluded for various reasons as illustrated in Figure **1**.

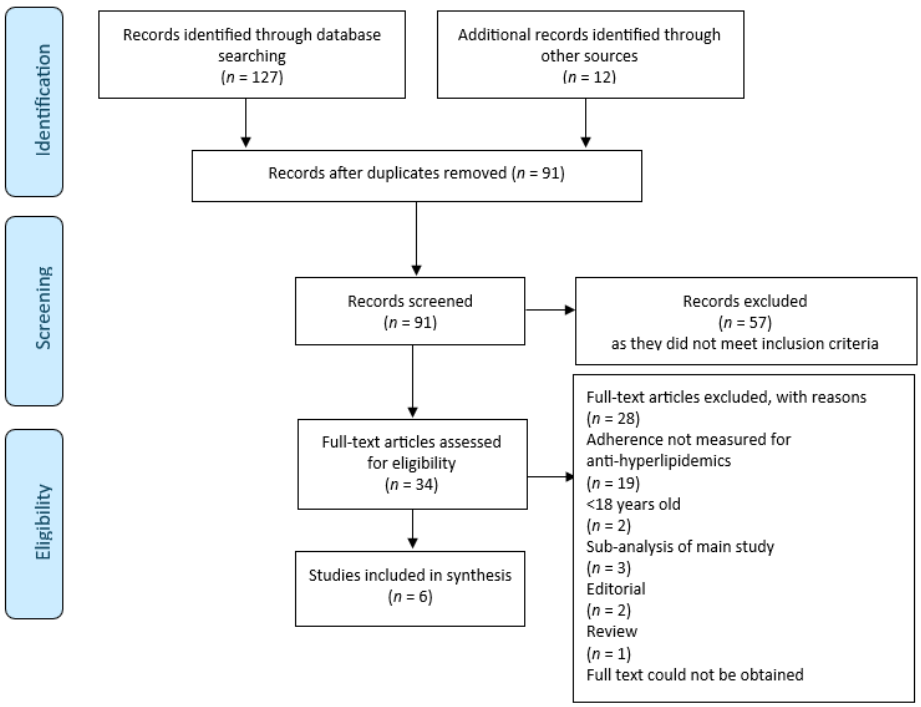

Figure 1: Systematic search in accordance with PRISMA guidelines.

Studies were then transferred to reference management software (Mendeley), manually screened, and shortlisted as per the inclusion and exclusion criteria. After selecting eligible articles, parameters like author information, publication year, study location, study aims, sample size and population, study design and tool, relevant findings, study limitations, and quality were highlighted. The papers included in the study were assessed using the Appraisal tool for cross-sectional studies, AXIS, (see Supplementary Material) for their quality and risk of bias [16].

3. Results

A total of 139 results from three databases and one search engine were returned, 34 studies were screened and six were deemed eligible for this review. All articles were cross-sectional studies of fair to good quality conducted between 2014 and 2023. Three of the papers were from Saudi Arabia, two from Kuwait and the UAE, and one study was conducted pan-GCC. The latter had a sample of around 5000 participants while the sample of other studies ranged between 200 and 1500. Three studies had aimed of measuring adherence to hyperlipidemia medications while the rest had it as a secondary objective. The location of the studies varied from tertiary hospitals, general practice, and cardiology clinics to diabetes centers. All except one study had the LLDs as exclusively statins. Adherence was measured differently through proportion ratios, adherence scales, pill counts, and a question related to forgetfulness in taking the pill. This led to results ranging from good adherence in two studies to low adherence in three studies, and indefinite results in the last study. Precise results are elaborated below, and the basic characteristics of the studies are summarized in Table **1**.

Table 1: Characteristics of the studies.

Author and Year	Study aim	Sample included (n) – population	Study design	Study tool	Study place	Relevant Results	Study limitations	Quality
Alharbi et al., 2023 [16]	The study aimed to assess the adherence to statins among diabetic patients and the factors related to neglect in compliance.	226 patients 18 years or above consenting diabetic patients prescribed statins.	Cross-sectional study that was retro-spective and descriptive. A question-naire was used to measure adherence.	Adherence was measured using the Morisky Medication Adherence Scale (MMAS-8) having three scores: < 6 indicating low adherence, 6-8 meaning medium adherence, and > 8 indicating high adherence levels.	Diabetic Center, Al Qassim region, Saudi Arabia	Results showed low, medium, and high adherence at 37.6%, 32.7%, and 29.7%, respectively. Lower age and diabetes duration were significantly associated with higher proportions of low adherence.	Single-center nature and low sample size limit extrapolation. Self-reported nature may introduce bias. The cross-sectional study design eliminates causality. Lack of data on reasons and patient characteristics related to non-adherence limit interpretation.	Good quality – 80%
Allaham et al., 2022 [17]	The study aimed to quantify the prevalence of medication adherence and asses the associated factors among patients with multimorbidities.	630 patients Adults aged ≥ 18 years with 2 or more morbidities attending clinics between February and September 2021.	Cross-sectional study using question-naires through a structured interview.	General Medication Adherence Scale (GMAS), which has four Likert scores and the sum of items categorizes adherence into low if the GMAS score is ≤ 26 and high if the GMAS score is ≥ 27.	Outpatient clinics, Rashid Hospital and Dubai Hospital, UAE.	The odds of medication adherence were 0.9 times lower in those with high cholesterol than those without, but it was not statistically significant. More than three-fourths of patients with a family history of dyslipidemia were adherent to medication.	Bias due to the self-reported nature of the study tool. Low generalizability because it was a2-center study. The authors also reported a lack of a qualitative methodology in the adherence tool.	Good quality – 84%

Table 1: Continued.

Author and Year	Study aim	Sample included (n) – population	Study design	Study tool	Study place	Relevant Results	Study limitations	Quality
Alwhaibi et al., 2019 [18]	The study aimed to explore the relationship of statin adherence with LDL levels and factors influencing this adherence in diabetic and dyslipidemia patients.	1532 patients Adult patients (≥18 years) with dyslipidemia and type-2 diabetes mellitus who were prescribed at least 2 fills of statin.	Cross-sectional that was retrospective and electronic health records based.	'Proportion of days covered' (PDC), which was calculated as total days of supply divided by days in follow-up. The patient was considered adherent if PDC ≥ 80%.	University-affiliated tertiary hospital, Riyadh, Saudi Arabia.	77.4% of patients with diabetes were adequately adherent to statin medications. Women, younger adults, and those with polypharmacy had lower odds of being adherent.	Being a single-center study, generalizability was low. Cross-sectional design affected causality. Not all confounders were measured.	Good quality – 82%
Al-Foraih and Somerset, 2017 [19]	The study aimed to examine the prevalence and factors related to statin adherence among patients with hypercholes-terolemia as well as the association of CHD risk with adherence.	200 patients Hypercholes-terolemic Kuwaiti adults aged between 30 and 69 years with hyperlipidemia diagnosis and at least 6 months of statin therapy.	Cross-sectional study using questionnaire and patient records (for confirmation).	The MMAS was used where a value of 8 is high adherence, 6 to <8 is medium and <6 is low.	12 general practice clinics across 4 governorates of Kuwait.	58.5% of patients had low adherence, 41.5% had medium adherence, and none had high adherence. Older age and diabetic status showed better adherence.	The authors do not mention any limitations, but the cross-sectional design may lower causality and increase bias.	Good quality – 70%
Al Shammeri et al., 2014 [20]	The study aimed to measure the rate of achieving optimal medical therapy (OMT). Among its components were adherence to LLDs and LDL cholesterol control.	207 patients CAD patients 18 years of age or above.	Cross-sectional study based on interviews, medical records, and electronic database.	Adherence to several medications (including statins) was measured usingpill counts and prescription claims.	Cardiology Clinic, Prince Sultan Cardiac Center, Qassim, Saudi Arabia.	Adherence to statins was at 94.3%. The most prevalent risk factor in CAD patients was dyslipidemia at 95%.	Single center investigation so it was a small study. Close follow-up and lipid profile of some patients was not done since they lived in different provinces.	Fair quality – 65%
Arafah et al., 2014 [21]	The study aimed to evaluate LDL cholesterol goal attainment for patients taking LLDs. One of the secondary objectives was to assess patient determinants for this goal achievement.	5276 patients ≥ 18 years on some form of LLDs for three or more months with no changes in dose for at least 6 months.	Cross-sectional: Centralized Pan-Middle East Survey	Adherence was measured through the following question in the survey: "approximately how often do you forget to take your cholesterol-lowering tablets?"	Outpatient clinics in Saudi Arabia, UAE, Qatar, Oman, Bahrain, and Kuwait.	32% of patients forgot to have their medication once a week or more. The majority of patients were on statins (94.4%) and the rest on other LLDs.	The authors do not provide results on the other answers for the frequency of forgetting to take pills and do not explicitly mention if compliance was good. Variability in clinic practice hindered extrapolation. Non-randomization of study participants limited study representativeness.	Fair quality – 63%

The first and most recent study, in 2023, was by Alharbi et al., [17] in the Al Qassim region of Saudi Arabia. The study aimed to assess statin adherence among 226 diabetics recruited from diabetes centers. Adherence was measured using the Morisky Medication Adherence Scale (MMAS-8) which is a self-reported 3-level questionnaire with high adherence, medium adherence, and low adherence. Results

revealed that two-thirds of patients had low or medium statin adherence at 37.6% and 32.7%, respectively, while 29.7% had high statin adherence. There was a statistically significant association between lower adherence to statins with younger age of under 50 years ($p = 0.009$) and lower duration of diabetes of < 5 years ($p = 0.029$). Similarly, a statistically significant difference in means of cholesterol and LDL among high adherence and low adherence patients was seen ($p = 0.001$ and $p = 0.025$, respectively), thus lipid profiles of patients who were compliant with statins were better. Finally, the authors reported study limitations in terms of sample size, self-report measures, and cross-sectional design.

The second study was in 2022 by Allaham et al., [18] in two tertiary hospitals in the UAE. The main aim of the study was to quantify the level of medication adherence and associated factors among patients with multimorbidity with one of the morbidities being dyslipidemia. The study included 630 patients and three survey tools consisting of demographic questions, the General Medication Adherence Scale (GMAS), and the self-administered co-questionnaire were used. The GMAS is an 11-item questionnaire with adherence measures related to patient behavior, pill burden, and payment. Findings indicated that the odds of medication adherence were 0.9 times lower in those with high cholesterol than with those who do not have high cholesterol (AOR = 0.941; CI [0.528, 1.678]), but it was not statistically significant (p-value = 0.837). Those with a family history of dyslipidemia had higher adherence at 76% and the self-reported control was indicated at 86%. Overall, the prevalence of high medication adherence among patients with comorbidity was around 78%. Finally, the study reported its limitations related to the self-reporting method, generalizability, and methodology.

The third study in 2019 was by Alwhaibi et al., [19] studying the association of statin adherence with the achievement of LDL cholesterol goal and factors related to compliance in patients with dyslipidemia and diabetes. Demographic, clinical, and prescription data were collected from electronic health records of adults who received at least two prescriptions of either simvastatin or atorvastatin from outpatient clinics in Riyadh, Saudi Arabia. Their adherence to statin therapy was measured using 'Proportion of Days Covered' or PDC ([total days supply/total number of days evaluated] × 100%). Adherence was a percentage equal to or more than 80%. Results showed out of 1532 patients included, 77.4% were adherent and 41.5% achieved the LDL target goal of < 2.6 mmol/L. Higher odds of adherence were seen in patients with no polypharmacy (AOR = 0.67, 95% CI: [0.47–0.96]), and lower odds of adherence were seen in women (AOR = 0.66, 95% CI: [0.49–0.87]) and those aged between 18 and 44 years (AOR = 0.58, 95% CI: [0.32–0.97]). However, hypothesis testing found no association between adherence to statin therapy and LDL target achievement. The authors attributed this to unmeasured confounders and the low generalizability of the study.

The fourth study was by Al-Foraih and Somerset [20], in 2017, in polyclinics across Kuwait. The researchers had three objectives: evaluate the prevalence of statin adherence, its associated factors, and the risk of coronary heart disease (CHD). 200 Kuwaiti adults were included who lived in rural or urban areas, diagnosed with hyperlipidemia, and given statins (atorvastatin, simvastatin, and rosuvastatin)

for at least 6 months before their first interview. Three questionnaires were utilized for data collection: a sociodemographic and clinical factors questionnaire, depression, anxiety, and stress scale, and the MMAS. Results indicated that 58.5% of patients had low adherence, 41.55 had medium adherence, and none had high adherence. Older age (OR = 1.05 [95% CI [1.01–1.09]) and being diabetic (OR = 0.42; 95% CI [0.23–0.75]) had better medium adherence. In terms of CHD, adherence to statins was inversely related to LDL cholesterol ($p < 0.01$). Finally, the study did not mention any limitations.

The fifth study was conducted in 2014 by Al Shammeri et al., [21] among CAD patients with the main objective of assessing the rate of achievement of optimal medical therapy (OMT) components; a part of this was adherence to cardiac medications like LLDs (statins) and LDL cholesterol control of < 100 mg/dL. A total of 207 consecutive adult patients in Al Qassim Province of Saudi Arabia who had CAD documented by noninvasive testing or by coronary angiogram clinic were recruited. Demographic data were collected from cardiologist interviews, clinical data was obtained from an electronic medical record database, and adherence was measured using pill counts and prescription claims. In terms of results, 10.4% achieved OMT and around 68% achieved the target for LDL cholesterol, but dyslipidemia was the prevalent risk factor for CAD patients at 95%. Authors reported high levels of medication adherence at 91% with adherence for statins at 94.3%; this percentage along with ACID/ARB medication was the lowest compared to aspirin, clopidogrel, and beta-blockers. Last, the main shortcoming listed was the nonavailability of lipid profiles in the files of most patients, and the inability to obtain the lipid profile of one-third of patients nor include it in the calculation for target achievement.

The final study was the Centralized Pan-Middle East Survey or CEPHEUS study done in outpatient clinics in the GCC region by Arafah et al., [22] in 2014. 5457 patients were included who were taking LLDs for at least 3 months with no recent dose changes. The main aim of the study was to evaluate the proportion of patients on LLDs attaining LDL cholesterol target goal as per the 2004 NCEP-ATP-III guidelines. The patients were asked to answer a questionnaire about hypercholesterolemia management and compliance, while physicians answered questions on patient demographics, LLD therapy, CVD history, body mass index, and metabolic syndrome status. The adherence was measured using a question to ask the patient on the frequency of forgetting to take LLDs, revealing 32% forget once or more per week. The majority of the patients were on statins, mainly atorvastatin followed by simvastatin and rosuvastatin. Regarding the main study aim, 48% of patients did not achieve LDL cholesterol goals. Limitations reported were small population, nonrandomization of participants, and lack of data collection on diet, socioeconomic status, and adverse events influencing compliance.

4. Discussion

This study set out to gather evidence on the adherence level to anti-hyperlipidemia medications in the GCC region within the last 10 years. There was limited research with only six studies being eligible and

three having the main aim of measuring adherence to LLDs. The adherence level varied across studies with good compliance seen in two Saudi studies at 77.4% and 94.3% measured through PDC, pill count, and prescription claims; adherence was lowest among all cardiac medications in the latter. Contrasting results were seen in an American study at 41.3% adherence using PDC [23] and an Iranian study at 79.7% compliance using the pill count method [24]. A plausible explanation for better adherence using pill counts in Saudi patients can be due to their CAD history, whereby, patients in the INTERHEART Middle East study taking LLDs rose from 5% before admission for myocardial infarction to 50% after discharge [25]. Similarly, a Malaysian scoping review posited that at least one hospitalization, CVD incident, or co-morbidity increases adherence [26]. Next, the two studies utilizing scales like MMAS in Kuwait and Saudi reported low adherence at 58.5% and 37.6%, respectively. While GMAS in the UAE study had 0.9 AOR, it was not statistically significant. Jordanian researchers reported better results using the MMAS at 32.8% low adherence [27]. Finally, the CEPHEUS study mentions that 32% of their participants forgot to take medications once or more per week, but it was difficult to compare since no data was presented on the other frequency levels. Such broad evidence was also seen in the Middle East with chronic disease drug adherence levels from 1.4% to 88% [10] and in Europe with statin adherence levels from 46% to 72% [28] due to the variation in the study tool.

Few factors were associated with low adherence to LLDs. There was consensus in three studies on lower adherence in younger age which is on par with the results of a cross-sectional analysis from Singapore [29], and a systematic review of developed countries [30]. Polypharmacy in one study was associated with lower compliance with matching findings from the Malaysian review [26]. Next, while two studies showed lower odds of adherence in women, one was not statistically significant. Unclear results on the association of gender with compliance were also seen in the scoping review from Malaysia [26] and a systematic review and meta-analysis from high-income countries [9].

In terms of LDL goal attainment, it was found to be low or suboptimal (in the studies that measured it) at 41.5%, 52%, and 68%. The World Heart Federation states that a majority of people around the world have suboptimal LDL cholesterol-lowering levels, one of the reasons being low adherence to LLDs [31]. While two studies in this review showed an inverse association between statin adherence and plasma cholesterol and LDL levels [20], another study found no association between statin adherence and LDL target achievement [19]. Limited evidence on the association between adherence and LDL cholesterol goal attainment was also seen in literature from Europe [28].

This study has the strength of being the first scoping review on adherence to anti-hyperlipidemia medications in the GCC region as far as the author's knowledge is concerned. Subsequently, the findings have implications for advancing public health practice and policy by enhancing hyperlipidemia management and understanding physician, medicine, or patient-related nonadherence factors. Policymakers can use this synthesis to review current health policies and ensure adherence to best-practice lipid management guidelines. Adherence trends and patterns can shape the bottom-up community empowerment

approaches and guide top-down awareness policies. All of these can be guided by artificial intelligence or machine learning for novel approaches to improve medication compliance.

Caution should be placed in translating these findings into practice due to the limitations of the cross-sectional design which has a risk for bias, lack of confounder control, unrepresentative sample, and causality issues. Also, indirect subjective tools used in the studies like self-report scales or interview-administered questionnaires may have a recall or reporting bias. Finally, one study was excluded from the review since its full-text version could not be obtained and grey literature was not examined, increasing publication bias.

5. Conclusion

This paper maps available evidence on anti-hyperlipidemia medication adherence among adults in the GCC region and factors related to non-adherence. Our results uncover a paucity of research, and varied compliance levels due to usage of different tools and highlight the role of age and polypharmacy in noncompliance. Gaps in the extent and type of literature act as a precursor for recommendations for higher evidence studies or randomized control trials. Future studies can utilize rigorous tools like the Medication Event Monitoring System, focusing on standardizing adherence measurements for hyperlipidemia patients and evaluating the role of gender on compliance. Also, future reviews can consider the newly emerging anti-hyperlipidemia injectables like PCSK9 inhibitors.

The recommendations to the government based on our finding of poor adherence are to standardize the tools used for measuring adherence; to conduct studies to assess reasons for nonadherence; and to organize targeted campaigns toward younger age for those with polypharmacy and females, as well as flag their clinical visits and tailor the counseling sessions to improve the adherence since they have been shown in some studies to have high nonadherence.

Finally, addressing research gaps on the level of adherence to anti-hyperlipidemia medication or the associated disparities can facilitate the prevention of poor prognoses like premature CVD mortality and morbidity in the Arabian Gulf region.

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Ethical Statement

The research is exclusively based on published literature; hence, ethical approval is not required.

Conflict of Interest

The authors declare that there is no conflicts of interest.

Artificial Intelligence (AI) Disclosure Statement

AI-unassisted work.

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Author Contribution

Conceptualization of or design of the work: L.A.A., J.N., A.T.R. Drafting the work and acquisition, analysis, and interpretation of data for the work: H.H.A. Critical Review of the work or quality check: A.T.R., L.A.A., J.N. All authors approved the final manuscript.

Data Sharing Statement

All data sets generated or analyzed during this study are included in the article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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