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Research Article

Medicine for novel therapy

Investigating the Incidence, Diagnosis, Prevention and Management of Statin-Induced Adverse Effects

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Abstract: Statin therapy reduces mortality associated with cardiovascular disease by preventing myocardial infarction and ischemic stroke. Despite the proven benefits of statins in this context, there is growing concern among patients and physicians regarding the safety of their short- and long-term use and adverse side effects, particularly muscle toxicity. As a result, non-adherence and withdrawal from treatment occur. This study is aimed to investigate the effectiveness of statin use in the secondary prevention of cardiovascular disease and diabetes in adults and the elderly by examining the incidence, diagnosis, prevention, and management of statin-induced adverse effects. A cross-sectional study of 350 patients using statins was conducted at King Abdulaziz and Hera'a General Hospital in Makkah. Data were retrieved from medical records and analyzed using SPSS software. The mean age of the sample population was 62±12 years old. Nearly 60% of patients had comorbidities, such as diabetes. However, statin treatment significantly decreased the levels of cholesterol, triglycerides, and low-density lipoprotein. Additionally, high-density lipoprotein levels were increased significantly, especially in patients with diabetes, indicating lower cardiovascular risk. The 2019 data showed that a high prevalence of patients used statin therapy. However, more than half of these patients achieved the low density lipoprotein treatment target. These results emphasize effective monitoring by physicians and patient adherence to the medications.

Keywords: Statins, Cholesterol, HDL, LDL, and Side effects.

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1. INTRODUCTION

Statins are 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors administered as therapy for lipid disturbances.[1,2,3] They control high lipid levels and lower low-density lipoprotein (LDL) as well as cholesterol.[2] Although they are considered first-line therapy, they cause various adverse effects.[3] Statins are associated with symptoms affecting multiple organs, such as the heart, liver, and muscles.[4] However, data from many clinical trials indicate that statins disturb glucose metabolism and increase the risk of developing diabetes.[5,6,7] In this study, we aimed to investigate whether statins are effective in the secondary prevention of cardiovascular disease and diabetes. Myopathy is a significant adverse effect of statins that contributes to poor adherence and therapy discontinuation.[8] Mostly, patients at the start of therapy complain of ambiguous muscle weakness, lethargy, or myalgia, leading to life-threatening rhabdomyolysis.[8] Although rhabdomyolysis is a serious adverse effect, it is quite rare.[9] In contrast, myalgia occurred in up to 10% of patients taking statins in previous observational studies.[10,11] Also, the possibility of adverse effects increases with high-intensity statin regimens. Statin-related muscular adverse effects were categorized into three levels to examine the mechanisms underlying the pathogenesis.[12] The first level is related to pharmacokinetics.[12] Some statins inhibit cytochrome P450-mediated hepatic biotransformation and hepatic uptake by transporter proteins, leading to increased levels of systemic statin concentrations.[5,12] Secondly, at the myocyte membrane level, cell membrane uptake transporters may help regulate intracellular statin concentrations.[6,13] Third, at the intracellular level, inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase can decrease the intracellular concentrations of downstream metabolites, such as selenoproteins, ubiquinone, and cholesterol. Moreover, this can induce changes in the gene expression of different factors, including ryanodine receptor 3 and glycine amidino transferase. [6, 14] Statins play a crucial role in reducing the incidence of cardiovascular complications in diabetes and pre-existing cardiovascular disease.[15] This directly influences both the prevalence and economic burden of cardiovascular complications and improves the mortality rates of patients .[16] Statins remarkably reduce the atherosclerosis rate due to a greater decrease in LDL-C and the inflammatory biomarker C-reactive protein (CRP).[8,9] Also, statin-treated patients with low CRP levels showed a minimum risk of chronic myocardial infarction or death related to coronary disorders.[17,18,19] Therefore, it is important to regularly and successfully manage the adverse effects of statins . Statins are used widely for the secondary prevention of cardiovascular complications, but their prophylactic use is also increasing. This study aimed to investigate the efficacy of statin use in the secondary prevention of cardiovascular disease and diabetes in adults and the elderly.

2. METHODS

2.1 Sampling methods

We collected data from patient medical records at King Abdulaziz Hospital and Hera'a General Hospital in Makkah Al-Mukarramah, and we sampled 350 patients. No need of consent because data were taken from the files not the patients. Ethical approval was obtained from IRB committee at College of Medicine, Umm Al-Qura University (ethical approval code: (HAPO-02-K-012-2021-02-518).

Patient selection

The medical records were assessed for the following information:

a- Diagnosis of hypercholesterolemia
b- The statin type prescribed
c- What were their lipid profiles after statin use?
d- What were their liver enzymes levels? before and after statin use?
e- What were their CK and FPG levels?
f- What side effects occurred that were associated with the use of statins?
g- What interventions reduced these side effects?
h- What medications managed these side effects?

2.2 Inclusion Criteria

- Patients aged 50–80 years
- Diagnosis of hypercholesterolemia
- Diagnosis of type 2 diabetes mellitus or coronary heart disease

2.3 Exclusion Criteria

Patients with no history of high cholesterol levels and children were excluded.

2.4 Privacy and protection of the data

The patients' IDs and names were not obtained for this study; we only assessed the medical information.

3 STATISTICAL ANALYSIS

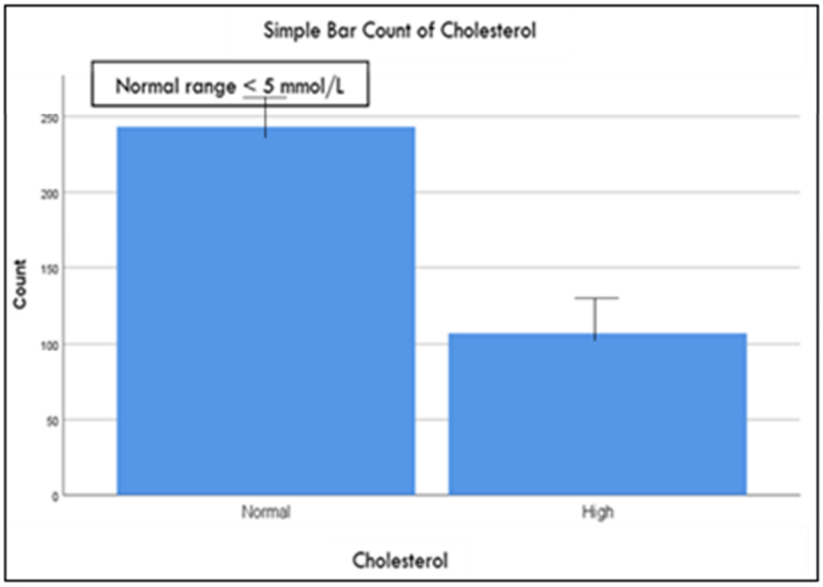
Data were analysed using SPSS 23.0 software 2015 with *P* value of < 0.05 is considered significant. Descriptive statistics were used to analyses frequency mean and percentages. Post-Hoc test was used to compare normal versus high values.

4 RESULTS

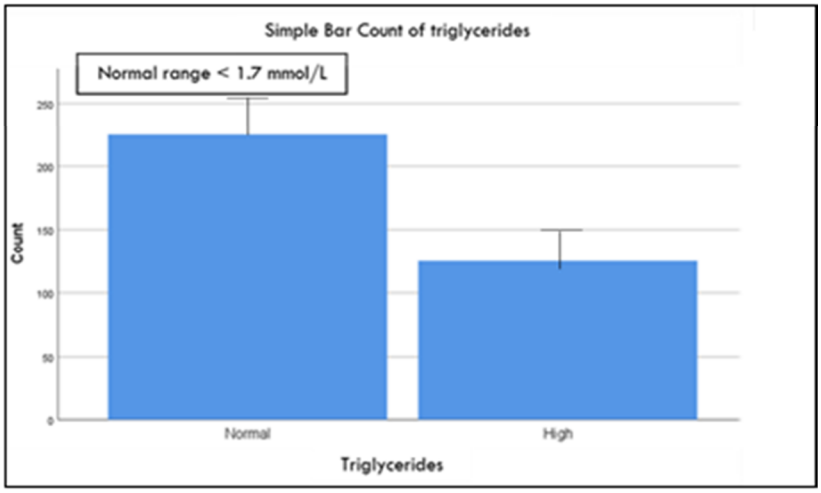
We selected 350 men and women with a mean (± SD) age of 62 ± 12 years from the medical records at King Abdulaziz Hospital (n = 175) and Hera General Hospital (n = 175). Approximately 60% of patients were males diagnosed with hypercholesterolemia, who received statins (especially atorvastatin or rosuvastatin 20 mg for at least three months) and had comorbidities, such as type 2 diabetes mellitus or coronary heart disease. We collected their most recent lipid profiles (HDL, LDL, TG, and CHOL) after statin use and their liver enzyme (AST, ALT) and creatine kinase (CK) levels. We calculated their CVD risk according to their age and cholesterol ratio. The primary outcome was to investigate the reduction in diabetes and cardiovascular disease risk following statin therapy. Statin therapy significantly decreased the levels of cholesterol, TG, and LDL. HDL levels were increased significantly, indicating reduced diabetes and cardiovascular disease risk. Patients' side effects included myopathy, myalgia, hyperuricemia, elevated liver enzymes (AST, ALT), and hypothyroidism. They received analgesics, vitamin D, and levothyroxine to manage these side effects. Graphs 1 to 5 show that statin therapy significantly decreased the levels of cholesterol, TG, and LDL. HDL levels were increased significantly, especially in patients with diabetes,

indicating a reduced cardiovascular risk.

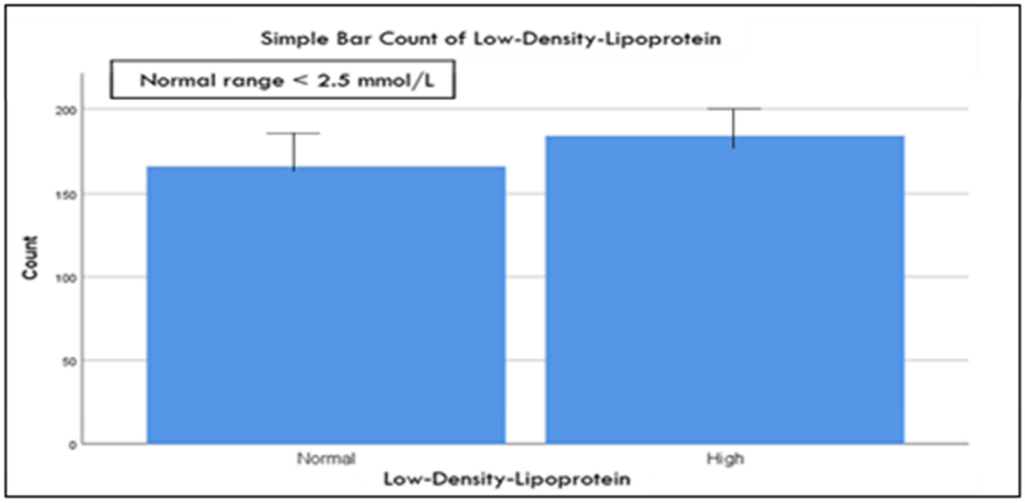
Table 1. Characteristics of Participants of the study in numbers and percentages. N=350	
Characteristic	
Age-Yr	**62 ±12**
Gender	
Male	**145 (40%)**
Female	**204 (60%)**
Type of statin	
Atorvastatin	**92 (26%)**
Rosuvastatin	**258 (74%)**
Previous Diseases	
Diabetes	**123 (35%)**
Cardiovascular Diseases	**227 (65%)**
Lipid profile	
Cholesterol	**4.4 ±1.3**
Triglycerides	**1.6± 1**
High- density lipoproteins	**1.1 ±0.3**
Low-density lipoproteins	**2.7± 1.1**
Other medications	
Analgesics	**149 (42.6%)**
Vitamin D	**95 (27.1%)**
Levothyroxine	**45 (12.9%)**



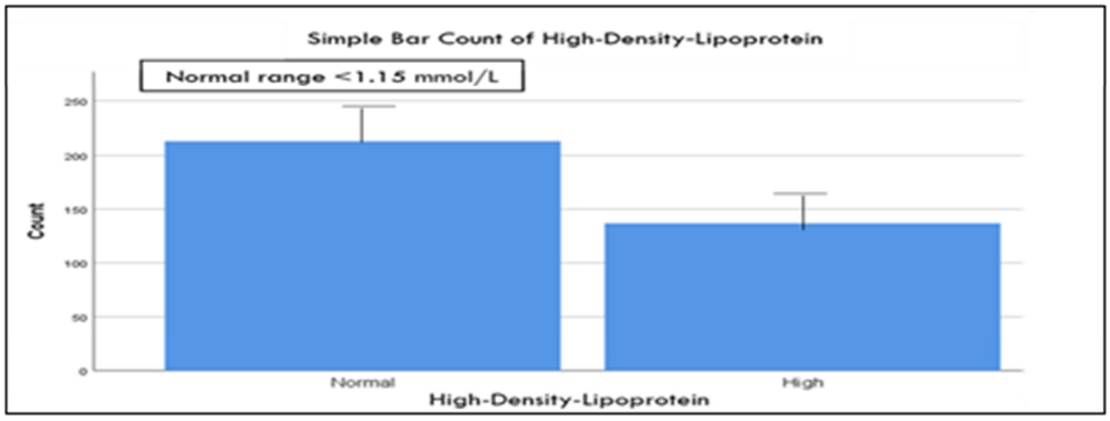
Graph 1 Chart representing the number of patients with normal and high cholesterol levels after statin therapy. (n = 350); t-test (P < 0.05). Results presented in mean±SD.



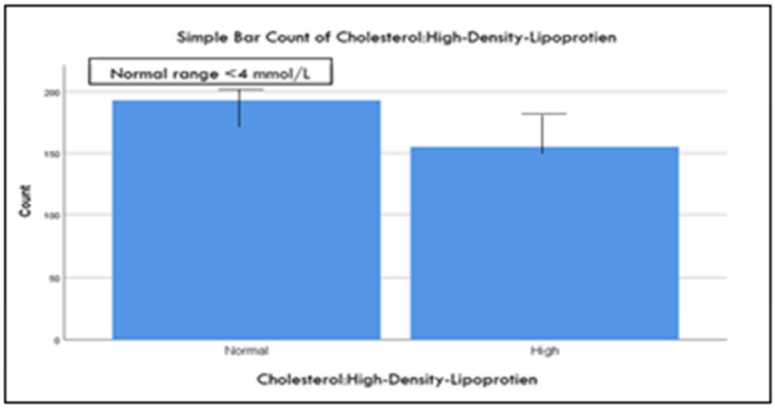
Graph 2 Chart representing the number of patients with normal and high triglyceride levels after statin therapy. (n = 350); t-test (P < 0.05). Results presented in mean±SD.



Graph 3 Chart representing the number of patients with normal and high levels of low-density lipoprotein (LDL) after statin therapy. (n = 350); t-test (P < 0.05). Results presented in mean±SD.



Graph 4 Chart representing the number of patients with normal and high levels of high-density lipoprotein (HDL) after statin therapy. (n = 350); t-test (*P* < 0.05). *Results presented in mean±SD.*



Graph 5 Chart representing the number of patients with normal and high cholesterol: high-density lipoprotein ratios after statin therapy. (n = 350); t-test (P < 0.05). Results presented in mean±SD.

5 DISCUSSION

It is well known that statin-associated symptoms are common, occurring in up to around 30% of patients in clinical practice. Recently, a Canadian working group outlined 6 key principles to manage patients with statin intolerance. This systematic approach ensures patients are appropriately receiving a statin and are aware of both the benefits and risks of therapy and addresses factors that may increase their risk of statin-associated Adverse effect. [17, 21] In our study we reported the number of adults and elderly patients with hypercholesterolemia whose conditions were associated with a comorbidity risk. These patients were on a stable daily dose of statin therapy for at least 90 days. We found a clinical

benefit in elderly patients who used statins for secondary prevention. However, we observed myopathy related to elevated CK levels and liver enzymes (no values presented in the manuscript), as well as hypothyroidism related to statin therapy. Hypothyroidism was treatable by administering levothyroxine. Moreover, continuous management and care were provided for patients with mild to moderate muscle pain or weakness, and their symptoms were managed with analgesics and vitamin D supplementation. Our data revealed statin therapy discontinuation when CK levels were more than ten times the normal level and accompanied by muscle pain or weakness that could result in the development of rhabdomyolysis, leading to muscle breakdown, myoglobinuria, and subsequent renal failure and death. During the three to five days after statin therapy discontinuation, we advise that if the CK levels remain high and the patient suffers from compartment syndrome, they may need surgical intervention. Furthermore, we advise that liver transaminase levels should be measured before and three months after initiating statin treatment to prevent complications because most liver abnormalities occur within that time. Then, liver transaminase levels should be measured periodically. Also, CK levels should be assessed, and the statin discontinued, at least temporarily, when a patient reports clinically significant myalgias or muscle weakness while on statin therapy. By reviewing the literature, we found that there were no similar studies available in Saudi Arabia. However, internationally, there are similar studies, but they differ in the study design.[17,18] These studies found that statin-induced side effects, including muscle aches, diabetes, and liver function test abnormalities, are recognized increasingly.[18,20] Moreover, they reported that statin-related muscle side effects are systematically classified and that statins increase the risk of the transition to diabetes in susceptible individuals with metabolic syndrome. Finally, there is little systematic evidence to link cognitive impairment with statin therapy.[18,19,20] The findings indicate that statins are the only drugs known to be both clinically beneficial and financially feasible for treating patients at high risk for CVD.[20] Several studies have reported that the cardiovascular advantages of statin therapy in high risk populations outweigh the limited negative consequences, such as the development of rhabdomyolysis.[15,19] Clinicians should make every effort to keep these patients on a statin- lipid- therapy and should not be alarmed by mild muscular symptoms or insignificant elevations in CK levels. To ensure long-term adherence, patients need to be sufficiently trained and adequately educated on the risks and benefits of statin use.

6 CONCLUSION

The results of our study were based on a representable population. Our findings demonstrate that statin therapy is an effective intervention for the secondary prevention of cardiovascular disease and diabetes. Significantly, we found a remarkable reduction in lipid profiles that effectively managed both diabetes and cardiovascular mortality. Also, the control of statin therapy-induced adverse effects was treatable with analgesics, vitamin D, and levothyroxine. The benefits of statin therapy exceeded the risks. Furthermore, there was high adherence of patients to their medications.

6.1 Limitations

There may be some limitations in this study, such as the control group and sample size, which may affect the internal validity. Due to a lack of data in the hospital records, we did not analyze some of the risk factors for CVDs, such as blood pressure parameters and smoking status, that may help us interpret our data and increase the quality of our findings.

6.2 Recommendations

Due to the widespread use of statins for reducing cholesterol and subsequent cardiovascular and diabetes mortality, in both primary and secondary prevention, further research on this topic is needed. Moreover, intensive education on interventions to increase the dose or add another statin to achieve the desired LDL-C target is required. Also, we need to raise awareness among patients regarding statin therapy and lifestyle modifications.

7 AUTHORS CONTRIBUTION STATEMENT

Yosra Alhind, Arwa Fiaraq and Sahar El-ashmony conceptualized and gathered the data with regard to this work. Ruzana Al-Hasani, Esraa Al-Matrafi, Renad Al-Harbi, Raneem Al Hazmi, Sarah Al-Hazmi and Jumana Saqqa analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript writing.

8 CONFLICT OF INTEREST

Conflict of interest declared none.

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