Prevalence of Side Effects, Drug Interaction among Patients Taking Statin in Turaif, Saudi Arabia

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Authors’ contributions

This work was carried out in collaboration among all authors. Author MAGR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors GHA and NAO managed the analyses of the study. Author MWA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Statins perceived to have favorable safety profile. Although many people on statin therapy do well but no drug is without potential for side effects. Awareness about risks as well as benefits of drugs is needed particularly drugs which are used on wide scale like statins because even uncommon side effects can have significant health impact.

Objectives of the Study: To determine side effects occurrence among Saudi patients taking statins and to evaluate drug-drug interactions in Saudi patients taking statins.

Methodology: Self administered cross sectional study conducted during a period of four months from October 2018 to January 2019 in Turaif general hospital, Saudi Arabia on random sample of 500 Saudi patients out of which 330 participants were included in the study which were taking different types of statins medication using self-administered questionnaire in Arabic language specially designed for the research purpose after obtaining verbal consent and the data analyzed by SPSS program.

Results: A total of 330 patients; 128 (39%) females and 202 (61%) males—participated in the study. The majority 165 (50%) were in the age-group of 50 – 59 years. Simvastatin was the most...
commonly used statin among study participants 136 (41%) followed by rosuvastatin 114 (35%). Among the participants, there were some patients who take drugs which have drug interactions with statins; there were 64 (19%) take Amlodipine with simvastatin, 13 (4%) and 6 (2%) take esomeprazole and omeprazole respectively with statins. Only 9 (3%) reported that they were advised by pharmacist to avoid grape fruit. Majority of participants 309 (94%) reported neck pain, difficulty in walking, frequently fatigue after starting on statin. Also majority of participants 320 (97%) suffer from muscle pain after starting statins medications.

**Conclusion:** The percentage of statin related side effects in this study population is high especially myopathy. Also some patients in this study taking medications that have drug interaction with statins, Counseling to patient regarding statin therapy appear to be insufficient. So, this study indicate that there’s a need for more efforts from the physicians and pharmacist to avoid prescribing or dispensing medication that have drug-drug interaction with statins and provide counseling to patients regarding their statin therapy.

**Keywords:** Statins; drug-drug interactions; simvastatin; omeprazole; counseling.

1. **INTRODUCTION**

Hydroxymethylglutaryl Co A (HMG-Co A) reductase inhibitors (statins) antihyperlipidemic medications have a many well documented benefits on cardiovascular diseases and atherosclerosis in many patient groups including male and female, young and old, at moderate risk and at severe risk for cardiovascular diseases. Also, benefits of statins have shown to exceed risks for mortality and morbidity specifically in clinical trials on middle aged men who were at risk for cardiovascular diseases [1-3]. Statins perceived to have favorable safety profile. [4-6] although many people on statin therapy do well but no drug is without potential for side effects. Awareness about risks as well as benefits of drugs is needed particularly drugs which are used on wide scale like statins because even uncommon side effects can have significant health impact.

Statins act by inhibiting HMG-Co A reductase enzyme early in mevalonate pathway [7] which generate cholesterol in addition to range of other substances such as coenzyme Q, heme-A and isoprenylated proteins [7] which play a vital roles in cell biology, physiological functions and also relevant to the beneficial and adverse effects of statins. Inhibition of cholesterol synthesis in liver by statins through inhibiting HMG-CoA reductase is significant because the internal synthesis of cholesterol through lever is higher than obtained externally through diet. Cholesterol synthesis in liver mostly occur during night, so statins mostly taken at night to maximize their effects. Previous studies have shown greater LDL and total cholesterol reductions in the short-acting simvastatin taken at night rather than the morning, but have shown no difference in the long-acting atorvastatin [8-10].

Additionally, cholesterol with its vital roles in the body is not only final product but also an intermediate to additional products which are fundamentally related to human health such as corticosteroids, bile acids, vitamin D and sex hormones and therefore these substances affected by administration of statins [11,12]. Statins have pronounced effects on lipid profile (low density lipoprotein [LDL], high density lipoprotein [HDL] and triglycerides [TG]) and also extend beyond to the direct products of mevalonate pathway to include other products and functions modified through nonmevalonate effects of statins, ranging from nitric oxide and inflammatory markers [13] to polyunsaturated fatty acids (PUFA) [14] among others.

Adverse effects of statin on muscle are the best recognized adverse effects of statins, perhaps the adverse effects on liver be the second most recognized adverse effects [15,16].

Statins are used for preventing and treating atherosclerosis that causes chest pain, heart attacks, strokes, and intermittent claudication in individuals who have or are at risk for atherosclerosis. There are many risk factors for atherosclerosis which include high cholesterol level, increasing age, family history and diabetes. Statins not used only for lowering cholesterol to normal level but also it can be used as a prophylaxis of atherosclerosis complications (e.g. heart attack, stroke, angina and death) which is
beneficial for people who have or at risk for atherosclerosis but haven't hypercholesterolemia to be candidate for statin therapy [17]. Experimental and clinical evidence indicates that statins exert additional beneficial effects via modulation of immune processes. Statins improve clinical outcomes in rheumatoid arthritis and heart transplantation, and reduce the number of inflammatory lesions in multiple sclerosis. Preliminary data indicate that statins might reduce cardiovascular morbidity and mortality in people with chronic kidney disease or diabetic nephropathy, as well as slowing disease progression [18]. Research continues into other areas where statins also appear to have a favorable effect, including dementia, lung cancer, nuclear cataracts, hypertension and prostate cancer [19,20].

2. RATIONALE OF THE STUDY

Statins are effective in lowering (LDL) cholesterol, but there are many factors like diet and genetics which may affect the action of these agents by decreasing it, or increasing their side effects. Although adverse effects of statins are serious especially with long-term use or co-prescription, no previous studies conducted in Saudi Arabia to examine the level of side-effects seen as result of statins use and the results of the present study will be useful for those who prescribe statins and will provide practical information from a familiar setting.

2.1 Objectives of the Study

- To determine side effects occurrence among Saudi patients taking statins.
- To evaluate drug-drug interactions in Saudi patients taking statins.

3. MATERIALS AND METHODS

3.1 Study Design, Duration and Setting

This was a Self administered cross sectional study conducted during a period of four months from October 2018 to January 2019 in Turaif general hospital- Saudi Arabia.

3.2 Study Population

Random sample of three hundred and thirty Saudi patients taking different types of statins medication with different ages range.

3.2.1 Inclusion criteria

- On any type of statins therapy
- Age is ≥20 years and ≤ 65 years
- Saudi in nationality
- Agree to fill the questionnaire

3.2.2 The exclusion criteria

- Age ≤ 20 years or ≥ 65 years
- Patients with diseases with symptoms look like statins side effects.
- Non-Saudi
- Patients who not gave consent or refuse to fill the questionnaire.

3.3 Data Collection and Data Collection Tool

The data was collected by using a self-administered questionnaire in Arabic language specially designed for the research purpose after reviewing related literature. The questionnaire consisted of thirty seven questions to obtain information about demographic characteristics, pattern of statin use, side effects interactions with statins, use of statin during pregnancy and lactation.

3.4 Statistical Analysis

After data collection, all variables entered, analyzed using SPSS program. Frequency tables and charts were used for descriptive statistics. The frequency and percentage calculated for all the participants demographics and answers for the questionnaire with representation for the answers by figures.

4. RESULTS

4.1 Demographic Characteristics of Study Participants

A total of 330 patients—128 (39%) females and 202 (61%) males—participated in the study. The majority 165 (50%) were in the age-group of 50 – 59 years. More than half 172 (52%) of the respondents had secondary education. 160 (48%) were governmental employee and 96 (29%) were private employee. The respondents were from Turaif city (Table 1).

4.2 Statins Use among Participants

Simvastatin was the most commonly used statin among study participants 136 (41%) followed by rosuvastatin 114 (35%). About 130 (39%)
prescribed dose of 40 mg and 112 (34%) prescribed dose of 20 mg. About two thirds of participants 211 (64%) use statin for more than six years while 82 (25%) use statin for four to six years. 286 (87%) of participants reported that physicians specified time for taking statin. When the respondents asked about the time for taking statin; 364 (82%) reported taking statin at bed time, 36 (11%) reported taking statin in the morning (Table 2).

### 4.3 Co-morbid Diseases and Other Drugs Used among Participants

Majority of 309 (94%) participants have co-morbid diseases, among them there were 265 (80%) with hypertension, 253 (77%) with diabetes and 137 (41%) with cardiac diseases. Majority of diabetic patients 248 (98%) started statin therapy after being diagnosed with diabetes. Among drugs used by study participants; 121 (37%) taking insulin, 89 (27%) taking glucophage, 102 (31%) taking lisinopril, 100 (30%) taking furosemide, 13 (4%) taking Esomeprazole, 6 (2%) taking Ompeprazole (Table 3).

Table 1. Demographic and socioeconomic characteristics of study participants (n=330)

| Variable       | Categories            | Frequency | Percentage (%) |
|----------------|-----------------------|-----------|----------------|
| Sex            | Male                  | 202       | 61%            |
|                | Female                | 128       | 39%            |
| Education      | Intermediate education| 42        | 13%            |
|                | Secondary education   | 172       | 52%            |
|                | University education  | 116       | 35%            |
| Age (years)    | 20-29                 | 2         | 1%             |
|                | 30-39                 | 7         | 2%             |
|                | 40-49                 | 49        | 15%            |
|                | 50-59                 | 165       | 50%            |
|                | 60-65                 | 107       | 32%            |
| Occupation     | Governmental          | 160       | 48%            |
|                | Private               | 96        | 29%            |
|                | Not employee          | 62        | 19%            |
|                | Retired               | 12        | 4%             |

Table 2. Statin use among study participants (n=330)

| Variable                        | Categories        | Frequency | Percentage (%) |
|---------------------------------|-------------------|-----------|----------------|
| Type of prescribed statin       | Atorvastatin      | 76        | 23%            |
|                                 | Simavastatin      | 136       | 41%            |
|                                 | Rosuvastatin      | 114       | 35%            |
|                                 | Fluvastatin       | 4         | 1%             |
| Dose of statin (mg)             | 10                | 32        | 10%            |
|                                 | 20                | 112       | 34%            |
|                                 | 40                | 130       | 39%            |
|                                 | 60                | 4         | 1%             |
|                                 | 80                | 52        | 16%            |
| Duration of statin use          | less than one year| 15        | 4%             |
|                                 | 1-3 years         | 22        | 7%             |
|                                 | 4-6 years         | 82        | 25%            |
|                                 | more than 6 years | 211       | 64%            |
| Specific time for taking statin specified by the physician | Yes | 286 | 87% |
|                                 | No                | 44        | 13%            |
| Time for taking statin          | At bed time       | 364       | 82%            |
|                                 | In the morning    | 36        | 11%            |
|                                 | During the day    | 21        | 6%             |
|                                 | When I remember  | 1         | 1%             |
Table 3. Co-morbid diseases and other drugs used among participants (n=330)

| Variable                                      | Categories     | Frequency | Percentage (%) |
|-----------------------------------------------|----------------|-----------|----------------|
| Other co-morbid diseases                      | Yes            | 309       | 94%            |
|                                               | No             | 21        | 6%             |
| Type of diseases among participants           | Cardiac diseases | 137       | 41%            |
|                                               | Hypertension   | 265       | 80%            |
|                                               | Diabetes       | 253       | 77%            |
|                                               | GIT disturbances | 72        | 22%            |
|                                               | Renal diseases | 2         | 1%             |
| If you are diabetic patient; when did you start taking statins? (n=253) | Before getting diabetes | 5 | 2% |
|                                               | After getting diabetes | 248 | 98% |
| Other drugs used with statins                 | Aspirin        | 53        | 16%            |
|                                               | Plavix         | 42        | 13%            |
|                                               | Metformin      | 29        | 9%             |
|                                               | Glucophage     | 89        | 27%            |
|                                               | Gliclazide     | 38        | 11%            |
|                                               | Insulin        | 121       | 37%            |
|                                               | Amlodipine     | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
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|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |
|                                               | Amlodipan      | 64        | 19%            |
|                                               | Enalapril      | 59        | 18%            |
|                                               | Captopril      | 33        | 10%            |
|                                               | Lisinopril     | 102       | 31%            |
|                                               | Perindopril    | 4         | 1%             |
|                                               | Fosinopril     | 42        | 13%            |

Table 4. Shows percentage of patients who take medications that interact with statins (n=330)

| Drug           | Frequency | Percentage (%) |
|----------------|-----------|----------------|
| Esomeprazole   | 13        | 4%             |
| Ompeprazole    | 6         | 2%             |
| Amlodipine     | 64        | 19%            |

4.4 Advises to Patients during Statin Therapy

Among the participants, there were 153 (46%) who visit the physician periodically, 129 (39%) patients always compliant with physician's advise and almost 39 (12%) patients not compliant with physician's advise. Majority of participants approximately 272 (82%) reported that they are advised by physician to avoid fats and their derivatives. Only 38 (11%) of the participated patients reported eating grape fruit or drink grape fruit juice and surprisingly only 9 (3%) reported that they were advised by pharmacist to avoid grape fruit (Table 5).

4.5 Patients Compliance with Statin

About one third 105 (32%) reported neglecting the statin dose, only 13 (4%) didn't take statin dose yesterday, about quarter of participants 86 (26%) reported that they forgot to take statin during last two weeks; among them there were 50 (58%) forget to take statin once and 32 (37%)
forget to take statin twice. Only 18 (5%) stopped statin due to worse feeling. Majority of participated patients 306 (93%) reported that they don't take their medications with them when they are travelling. 29 (9%) reported that they stopped taking statin when their lipid level is under control. Among the participants there were 46 (14%) have difficulties in compliance with lipid lowering regimen. More than half of participants 175 (53%) reported that they sometimes have difficulties in remembering daily dose of statin (Table 6).

### 4.6 Heart Attack during Statin Use

More than one third 130 (39%) of participants reported disturbances during statin use. Moreover 119 (87%) patients reported to experience heart attack for once during statin therapy and only 7 (5%) patients reported to experience heart attack for three or more times during the statin therapy (Table 7).

### 4.7 Side Effects of Statins among Participants

Regarding side effects, majority of participants 309 (94%) reported neck pain, difficulty in walking, frequently fatigue after starting on statin. Also majority of participants 320 (97%) suffer from muscle pain after starting statins medications. However, only 12(4%) of participants reported experience change in urine color after initiation of statins medications. Only 15 (29%) of the patients who experienced side effects from statin told their physician about the experienced side effects. The physician advised 7 (46%) of them to decrease statin dose, 3 (20%) Changed to other medication, 12 (80%) of them Continued to take medication with addition of other medication to treat the symptoms. Diclofenac sodium was the major drug added by physician to treat side effects of statin 12 (80%) Figs.1 and 2.

### 4.8 Investigations and Follow Up for Patients on Statin

Majority of participants 311 (94%) advised by physician to investigate liver enzymes every 3 to 6 months. During follow up visit; 317 (97%) perform lipid panel, 151 (46%) perform liver function test and 280 (86%) perform Hb A1C (Table 8).

### 4.9 Female Use of Statin during Pregnancy or Lactation

More than half of participated female patients reported that they were not advised by physician or pharmacist to stop statins during pregnancy or lactation and two (3%) of them reported using statins during pregnancy or lactation (Fig. 3).

| Table 5. Advises to patients during statin usage (n=330) |
|---------------------------------------------------------|
| **Variable**                                            | **Categories**                  | **Frequency** | **Percentage (%)** |
|---------------------------------------------------------|
| Doctor visit                                            | Periodical                      | 153           | 46%               |
|                                                        | Not periodical                  | 160           | 48%               |
|                                                        | When diseased                   | 15            | 4%                |
|                                                        | When feeling any side effect of | 2             | 1%                |
|                                                        | the medicine                    |               |                   |
| To what extent are you compliant with doctor advise?    | Always compliant                | 129           | 39%               |
|                                                        | Sometimes compliant             | 162           | 49%               |
|                                                        | Not compliant                   | 39            | 12%               |
| Did the doctor advised you to avoid fats and fat        | Yes                            | 272           | 82%               |
| derivatives?                                            | No                             | 58            | 18%               |
| Do you eat grape fruit or drink grape fruit juice?      | Yes                            | 38            | 11%               |
|                                                        | No                             | 322           | 98%               |
| Did you advised by physician or pharmacist to avoid     | Yes                            | 9             | 3%                |
| grape fruit?                                            | No                             | 321           | 97%               |
| Have you subjected to heart attack or disturbances      | Yes                            | 130           | 39%               |
| during taking statins?                                  | No                             | 200           | 61%               |
| Frequency of heart attack or disturbances during         | Once                           | 119           | 87%               |
| taking statins? (n=130)                                  | Twice                          | 11            | 8%                |
|                                                        | Three times                     | 6             | 4%                |
|                                                        | More than three times           | 1             | 1%                |
Table 6. Patients compliance with statin (n=330)

| Variable                                                                 | Categories | Frequency | Percentage (%) |
|-------------------------------------------------------------------------|------------|-----------|----------------|
| Do you sometimes forget to take statins?                               | Yes        | 105       | 32%            |
|                                                                          | No         | 225       | 68%            |
| Did you take your statin yesterday?                                    | Yes        | 317       | 96%            |
|                                                                          | No         | 13        | 4%             |
| During the last two weeks, did you forget to take statin?              | Yes        | 86        | 26%            |
|                                                                          | No         | 244       | 74%            |
| If you forget to take statin during last two weeks, how many times?    | Once       | 50        | 58%            |
|                                                                          | Twice      | 32        | 37%            |
|                                                                          | Three times| 1         | 1%             |
|                                                                          | Four times | 1         | 1%             |
|                                                                          | Five times | 2         | 2%             |
| Have you ever stop statin due to feeling worse?                         | Yes        | 18        | 5%             |
|                                                                          | No         | 312       | 95%            |
| Do you take your medication with you when you travel?                  | Yes        | 24        | 7%             |
|                                                                          | No         | 306       | 93%            |
| Do you stop taking statin when your lipid level is under control?      | Yes        | 29        | 9%             |
|                                                                          | No         | 301       | 91%            |
| Have you any difficulties in compliance with lipid lowering regimen?    | Yes        | 46        | 14%            |
|                                                                          | No         | 284       | 86%            |
| To what extent do you have difficulties in remembering your daily dose | Often      | 10        | 3%             |
|                                                                          | Sometimes  | 175       | 53%            |
|                                                                          | Rarely     | 144       | 44%            |

Table 7. Heart attack during statin use (n=330)

| Variable                                                                 | Categories | Frequency | Percentage (%) |
|-------------------------------------------------------------------------|------------|-----------|----------------|
| Have you subjected to heart attack or disturbances during taking statins| Yes        | 130       | 39%            |
|                                                                          | No         | 200       | 61%            |
| Frequency of heart attack or disturbances during taking statins (n=130) | Once       | 119       | 87%            |
|                                                                          | Twice      | 11        | 8%             |
|                                                                          | Three times| 6         | 4%             |
|                                                                          | More than three times | 1 | 1% |

Table 8. Investigations and follow up for patients on statin (n=330)

| Variable                                                                 | Categories        | Frequency | Percentage (%) |
|-------------------------------------------------------------------------|-------------------|-----------|----------------|
| Did your physician advised you to investigate liver enzymes every 3 to 6 months? | Yes               | 311       | 94%            |
|                                                                          | No                | 19        | 6%             |
| Investigations during follow up visit                                    | Lipid panel       | 317       | 97%            |
|                                                                          | Liver function tests | 151       | 46%            |
|                                                                          | Hb A1C            | 280       | 86%            |

5. DISCUSSION

In this study 39% of patients were females mainly above 50 years old; that may be due to decrease in oestrogen level, the hormone which have an important role in decreasing cholesterol level and consequently reduce risk of cardiovascular diseases. Many studies have reported that the incidence of coronary heart diseases in postmenopausal women is higher than that of premenopausal women of the same age range, one reason for this apparent protection from coronary heart disease in premenopausal women is thought to be circulating sex hormones, in particular oestrogens, which decrease rapidly after menopause [21-29].
Fig. 1. Side effects of statins among participants

| Side Effect                                                                 | Yes (%) | No (%) |
|-----------------------------------------------------------------------------|---------|--------|
| Suffering from pain in neck, difficulty in walking, frequent fatigue after starting on statin | 90      | 10     |
| Suffering from muscle pain after starting statins medications               | 10      | 90     |
| Experiencing change in urine color after initiation of statins medications  | 30      | 70     |
| Told physician about the side effects                                       | 40      | 60     |

Fig. 2. Physician's intervention to statin related side effects

| Physician's advice regarding side effects | Decrease dose | Change to other medication | Continue to take medication with addition of other medication to treat the symptoms | Didn't put into consideration | Diclofenac sodium | Other |
|------------------------------------------|---------------|---------------------------|---------------------------------------------------------------------------------|-------------------------------|------------------|-------|
| The medication added to treat side effects| 50            | 20                        | 30                                                                               | 10                            | 20               | 10    |
Atorvastatin has also been studied with “high increases the mean AUCs of simvastatin and dose grapefruit juice” (6 glasses per day) found in previous study which said that “High avoid grape fruit which also may be a cause for physicians and pharmacists didn’t advise them to their physicians to avoid fat and their derivatives, related to statins like myopathy and consequently rising probability of side effect their concentration in the blood stream and inhibiting their metabolism lead to increase of long and short term therapies interact with statins such as Amlodipine and also some patients were using long term therapy with simavastatin is the most common statins Rosuvastatin (35%) which indicate that In this study, the most commonly used statins were simavastatin (41%) followed by Rosuvastatin (35%) which indicate that simavastatin is the most common statins prescribed in Saudi Arabia. In this study, 19% of patients were using long term therapy with statins such as Amlodipine and also some participants use short term therapy such as ompeprazole (2%), esomeprazole (4%). Both long and short term therapies interact with actions of atorvastatin and simvastatin by inhibiting their metabolism lead to increase of their concentration in the blood stream and consequently rising probability of side effect related to statins like myopathy and rhabdomyolysis [28].

82% of patients in this study were advised by their physicians to avoid fat and their derivatives, but 97% of total patients in this study their physicians and pharmacists didn’t advise them to avoid grapefruit which also may be a cause for complaining from myopathy due to the inhibiting effect of grapefruit on cytochrome P450 3A4. As found in previous study which said that “High-dose grapefruit juice” (6 glasses per day) increases the mean AUCs of simvastatin and simvastatin acid 16-fold and 7-fold, respectively, with the mean AUC of active HMG-CoA reductase inhibitor increasing 2.4- to 3.6-fold. Atorvastatin has also been studied with “high dose juice” with the AUC of active and total HMG-CoA reductase inhibitors increased 1.3- and 1.5-fold [30]. Another study said that taking the juice (e.g. 240 ml of grapefruit juice) in the morning and then the statin in the evening to avoid the interaction, as little as one glass of grapefruit juice can cause the interaction and pharmacokinetic studies have shown the enzyme inhibition can last for three days or more in healthy patients. It would therefore be prudent to avoid drinking grapefruit juice altogether [31].

39% of patients in this study were exposed to heart problem which may be due to delayed action of statins in preventing heart attack. 97% of study population complain from myopathy, 94% suffering from neck pain, difficulty in walking, frequent fatigue which may be partly due to drug-drug interaction with statins. There are reports of patients treated with atorvastatin or simvastatin (more than 1 year) who developed myopathy or rhabdomyolysis following the addition of esomeprazole (6 weeks). The patient reported the experiencing symptoms of increased fatigue, mild chest pain, and shortness of breath that coincided with the initiation of esomeprazole approximately six weeks prior to admission [32]. From 1987 to May 2001 the Food and Drug Administration recorded 42 deaths from rhabdomyolysis attributable to statins in the United States [32]. It is reported that early recognition of muscle toxicity can prevent progression to most serious complication of rhabdomyolysis and renal failure [33]. 8% of patients using statins for less than one year suffered from statin related myopathy as
study said that statin related myotoxicity can occur suddenly, weeks or months after the drug has been initiated.

Majority of patients who reported side effects of statins in this study were old aged as found in the previous study that several clinical conditions appeared to predispose patients to myopathy including advanced age [33]. 29% of patients suffered from myopathy symptoms told their physicians about these symptoms, 20% of patients their physicians concluded these symptoms were a result of statins medication and shifted them to another type of statin therapy, 80% of the remaining patients their physicians put them on analgesic therapy like diclofenac sodium, which mask symptoms and prevent early diagnosis. It has been reported that early recognition of muscle toxicity can prevent progression to most serious complication of rhabdomyolysis and renal failure.

The risk of teratogenicity of statins, if any, appears to be relatively small in some studies [34,35] given the scarcity of available data, it is still advisable to avoid use of statin drugs in patients who are planning pregnancy in order to reduce the risks as much as possible. However, more than half of the female in this study reported that they were not advised by physician or pharmacist to stop statin during pregnancy and lactation which may be due to their old age and two of them reported using statins during pregnancy or lactation.

6. LIMITATIONS OF THE STUDY

The study is limited by its small number sample and cross sectional design, that patients who are treated in private clinics were not included and the present study was single institutional based, hence results may not be extrapolated to general population.

7. CONCLUSION

The percentage of statin related side effects in this study population is high especially in case of myopathy and some patients also showed the drug interaction with statins making them more susceptible to rhabdomyolysis and resulting in renal failure. This study indicate that counseling alone cannot be very helpful, there's a need for more efforts from the physicians and pharmacist to avoid prescribing or dispensing medication that have drug-drug interaction with statins.

8. RECOMMENDATIONS

- Pharmacists must be more attentive and updating their information's to any drug drug interactions in the prescription.
- Clinical pharmacists and physicians must take into account the muscle problems related to statin therapy which may be progress to rhabdomyolysis and consequently renal failure if it is misdiagnosed.
- Patients should be encouraged to report any an abnormal symptoms to health care providers and advised to be compliant with medication instructions.

CONSENT
Consent obtained from each participant before answering the questionnaire and the confidentiality of the data obtained assured.

ETHICAL APPROVAL
As per international standard or university (Northern Border University) standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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