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Cohort Study

Statin Induced Myopathy Among Patients Attending the National Center for Diabetes, endocrinology, & genetics

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ABSTRACT

Background and objectives: myopathy is a major side effect of statins that leads to statin intolerance and discontinuation. In this prospective cohort study, the main objective was to estimate the incidence of myopathy in patients receiving statins. In addition, we identified some risk factors associated with statin induced myopathy.
Methods: A prospective cohort study was conducted at the National Center for Diabetes, Endocrinology and Genetics [NCDEG] in Jordan from October 1, 2018 to January 31, 2021. All subjects who initiated statin therapy followed up during that period. Data was collected at time 0 (baseline), 3, 6, 9, and 12 months after enrollment. Demographic and clinical data were collected from medical records. Muscular symptoms were collected by conducting face-to-face interviews to all patients using a pre-structured questionnaire.
Results: The overall incidence of myopathy among patients taking statins was 27.8%, 31.4% in males and 22.6% in females, the incidence of myopathy was higher in older people, being highest in patients ≥60 years (34%). Bivariate analyses showed no significant association between myopathy and hypothyroidism, diabetes or medications that are known to interact with statins. The incidence of myopathy was highest with Simvastatin 40 mg (50%) and lowest with Fluvastatin XL 80 mg (8%) and Rosuvastatin 10 mg (10.8%).
Conclusions: The overall incidence of myopathy in patients taking statins was 27.8%. Myopathy was directly related to dose and type of statin used. The use of Fluvastatin XL 80 mg and Rosuvastatin 10 mg showed less incidence of myopathy compared with other statins.

1. Introduction

Cardiovascular diseases are considered the leading cause of morbidity and mortality worldwide, with the major cause being the formation of lipid plaques in coronary arteries. High plasma level of total cholesterol and low-density lipoprotein (LDL) are well-established risk factors for ischemic heart disease [1,2]. Statins (HMG-CoA Reductase Inhibitors) have proven to efficiently lower serum concentration of total cholesterol and LDL. Apart from lipid lowering properties, statins have also other beneficial effects on cardiovascular events, including improvement of endothelial function, reduction of smooth muscles proliferation, and modification of inflammatory responses. Accordingly, statins are considered a cornerstone in both the primary and secondary prevention of cardiovascular diseases [3–5].

Statins are generally safe and well tolerated; however, they can be associated with various adverse effects. Myopathy is recognized as the most common adverse effect associated with statin therapy [6], ranging from myalgia (muscle symptoms without creatinine kinase elevation) to myositis (muscle symptoms with increased creatinine kinase level). In rare situations, it can worsen to life threating rhabdomyolysis (muscle symptoms with marked elevation of creatinine kinase and myoglobinuria) [7]. The incidence of statins induced myopathy reported in previous studies ranged from 5% to 20% dependent on the criteria of diagnosis of myopathy and the type of study [8–12]. Since adherence to statin therapy can be limited by myopathy, and given the more aggressive approach to lipid-lowering therapy advocated by recent treatment guidelines, better understanding of the nature of statin induced myopathy is of considerable importance [13,14].

The main objective of this study is to estimate the incidence of myopathy in patients receiving statin therapy over 12 months of follow-

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up. In addition, we explored a possible association between myopathy and a number of factors that may increase that risk.

2. Subjects and methods

This prospective cohort study was conducted at the National Center for Diabetes, Endocrinology, and Genetics (NCDEG) in Amman, Jordan, from October 1, 2018 to January 31, 2021. All adult patients, 18 years old or above, who initiated statins therapy during the above-mentioned period were invited to participate in the study. Clinical charts, nursing records, and laboratory findings were reviewed. Demographic data, medical history, underlying comorbidities, medications profile, and laboratory findings were extracted. The type and dose of statin used, and other concomitant medications, with particular consideration of drugs known to interact with statins were obtained.

All patients were interviewed by the principle author using a pre-structured questionnaire. The questionnaire included onset, nature, and location of muscle symptoms after statin therapy initiation, in addition to life style factors including degree of exercise, dietary habits and alcohol intake. The questionnaire and laboratory investigations, including creatine kinase (CK) level, lipid profile, thyroid function tests, vitamin D level, liver function test, and creatinine level were conducted at baseline before starting statin therapy and repeated at months 1, 3, 6, and 12 after initiation of statin therapy.

We adapted the American College of Cardiology (ACC), the American Heart Association (AHA), and the National Heart, Lung, and Blood Institute (NHLBI) for myopathy and related terms definitions [15]. .

The incidence of Statin-induced myopathy was calculated by dividing the number of patients who developed muscular symptoms and/or CK elevation after starting statin therapy to the total number of patients.

All patients who had muscular pain prior the initiation of statin, creatinine level more than two mg/dl (normal range 0.5–0.9 mg/dl), alanine transaminase (ALT) level more than two times the upper limit of normal (normal range 0–33 mg/dl), inherited or metabolic muscle or joint diseases were excluded.

3. Ethical considerations

An informed consent was obtained from the recruited patients. All procedures performed in this study involving human participants were reviewed and ethically approved by the Institutional Review Board (IRB) and research and ethics committee at NCDEG, Amman, Jordan. This study was conducted following the 1975 Helsinki declaration, as revised in 2008 and its later amendments or comparable ethical standards.

4. Statistical analysis

Data was entered and analyzed using the Statistical Package for Social Science (SPSS version 21). The overall incidence of myopathy was calculated as well as the incidence in subgroups defined by relevant variables. The bivariate association between myopathy and a number of variables was assessed for statistical significance using the chi square test. A P-value of <0.05 was considered statistically significant.

5. Results

The population of our study was 465 subjects, 400 completed the study (59.0% males and 41.0% females) with a mean age ± SD of 54.2 ± 10.3 years. The remaining 65 patients dropped out due to poor compliance or lost follow up.

Their demographic information and clinical characteristics are summarized in Table 1. The most common age group was between 50 and 59 years old (41%). Most of the patients in this study were either obese or overweight (87%), and the mean (SD) BMI for the study participants was 32.2. Around 70% of the studied population were nonsmokers, while 21% were current smokers. Sixty nine percent of patients were diabetics, 53% were hypertensive, 7.8% had coronary artery diseases, 12.8% had hypothyroidism and 3% had osteoporosis (see Table 2).

Table 1
Clinical spectrum of statin induced myopathy.

Terminology	Definition
Myalgia	Muscle pain or weakness without elevated creatine kinase
Myositis	Muscle symptom with elevated creatine kinase, typically less than 10 times the upper limit of normal.
Rhabdomyolysis	Muscle symptom with elevated creatine kinase, typically more than 10 times the upper limit of normal
Asymptomatic myopathy	Elevated creatine kinase without muscle symptom
Statin induced myopathy	Development of muscular symptoms with or without CK elevation or isolated CK elevation without muscular symptoms after initiating statin therapy.

Table 2
Characteristics of study participants (n = 400), Jordan, 2021.

Characteristics	NO. (%)
Gender	
Female	236 (59.0)
Male	164 (41.0)
Age (years), mean ± SD = 54.2 ± 10.3	
< 40	38 (9.5)
40-49	79 (19.8)
50-59	164 (41.0)
60-69	94 (23.5)
≥ 70	25 (6.3)
BMI (kg/m^2), mean ± SD = 32.2 ± 15.9	
Normal (18.5–24.99)	49 (12.3)
Overweight (25–29.99)	121 (30.3)
Obese (≥30)	230 (57.5)
Smoking	
Current smoker	85 (21.3)
Past-smoker	36 (9.0)
Nonsmoker	279 (69.8)
Co-morbidity	
Diabetes Mellitus	276 (69.0)
Hypertension	212 (53.0)
Coronary Artery Diseases	31 (7.8)
Hypothyroidism	51 (12.8)
Osteoporosis	12 (3.0)

The overall incidence of statin induced myopathy was 27.8% (n = 111). Evaluation of myopathy with respect to gender and age groups is depicted in Table- 3. Although there was no significant association between myopathy and gender, myopathy was more prevalent in males (31.4%) in comparison to females (22.6%). The incidence of myopathy increased with increased age, In age group 40–49 years, 26.6% developed myopathy, in 50–59 age group, 28.7% developed myopathy, whereas in 60–79 age group, 34.0% developed myopathy but without significant association between age and incidence of myopathy.

During the observation period, the incidence of myopathy was found to be in 81 (20.2%), 39 (9.8%), 13 (4.5%) and 7 (3.8%), respectively during the observation period (1, 3, 6 and 12 months) (see Table 3).

Presence of myalgia with respect to dose of statin is depicted in Table 4. Incidence of myopathy in patients who took Fluvastatin XR 80 mg was the lowest (8%), whereas the highest incidence of myopathy was among the group who took simvastatin 40 mg (50%).Rosuvastatin 10 mg had the lowest risk of myopathy after Fluvastatin (10.8%) whereas the incidence of myopathy in patients who took Rosuvastatin 20 mg was 14.6%. The incidence of myopathy for atorvastatin 10 mg, 20 mg, 40 mg was 12,5%, 21,2%, and 28,9% respectively (see Table 5).

No significant differences were found in risk factors associated with statin induced myopathy in terms of hypothyroidism, diabetes mellitus, Ca channel blockers, Allopurinol and Fibrate as shown in Table 4.

Table 3
Types and doses of statins, Jordan, 2021.

Types of statins	NO. (%)
Rosuvastatin	
10 mg	62 (15.5)
20 mg	32 (8.0)
Atorvastatin	
10 mg	24 (6.0)
20 mg	154 (38.0)
40 mg	37 (9.3)
Simvastatin	
20 mg	72 (18.0)
40 mg	7 (1.8)
Fluvastatin XL	
80 mg	12 (3.0)

Table 4
Incidence of myopathy by selected variables and the significance of observed differences, Jordan, 2021.

Variables	Presence of Myopathy No. (%)	P-value
Gender		
Female	37 (22.6)	0.053
Male	74 (31.4)	
Age (years)		
< 40	5 (13.2)	0.185
40-49	21 (26.6)	
50-59	47 (28.7)	
60-79	38 (34.0)	
BMI (kg/m^2)		
Normal (18.5–24.99)	13 (26.5)	0.477
Overweight (25–29.99)	29 (24.0)	
Obese (≥40)	69 (30.0)	
Hypothyroidism	12 (23.5)	0.471
Diabetes mellitus	82 (29.7)	0.191
Ca channel blocker	12 (21.4)	0.255
Allopurinol	5 (33.3)	0.623
Fibrate	8 (42.1)	0.152

Table 5
Incidence of myopathy according to dose and type of statin treatment Jordan, 2021.

Statin	Presence of Myopathy No. (%)
Rosuvastatin	
10 mg	16 (10.8)
20 mg	7 (14.6)
Atorvastatin	
10 mg	5 (12.5)
20 mg	46 (21.2)
40 mg	13 (28.9)
Simvastatin	
20 mg	20 (25.3)
40 mg	4 (50.0)
Fluvastatin XL	
80 mg	1 (8%)

6. Discussion

Our study showed that the overall incidence of statin induced myopathy was 27.4%. This confirms the findings of previous studies that statins cause myopathy. However the incidence of myopathy in our study was much higher compared to most previous reports [7–11]. This also suggests that the incidence rate of statin induced myopathy, observed in randomized clinical trials (1–5%), may underestimate the actual rate of this side effect and may not be generalized to community based clinical practice settings [7,8], this may be explained by the inclusion criteria where patients with comorbidities that would predispose to an increased risk of statin induced myopathy may be underrepresented in these trials.

The effect of statins on muscle performance study [16], was the only randomized, double blind, placebo-controlled study that evaluated the effect of statins on skeletal muscle symptoms and performance, 420 subjects were randomized to atorvastatin 80 mg daily or placebo for 6 months. The incidence of myopathy was 9.4% of the statin-treated and 4.6% of control group, which is higher than most other randomized controlled trials but less than that reported in observational trials.

Our results are also higher than that reported by most other studies worldwide such as the PRIMO study [9], Gregory et al. study [10], and Skiliving et al. study [11], where muscular symptoms were in the range of 10–15%. However, myopathy, in our study, was somewhat lower than the 33% reported by the Heart Protection Study over 5 years [17].

In Jordan, our results are consistent with Yazan et al. [18], which was a cross sectional retrospective study conducted on about one thousand subjects, 27.9% of them developed muscular symptoms, and with Elsalem et al. [19], a prospective comparative study on 345 patients receiving statins and compared the findings with age-and gender-matched control group of 85 subjects, and reported a relatively high rate of muscular symptoms among patients using statins (21%).

The relatively high rate of statin induced myopathy in our population found in these studies may point to the importance of genetic factors, cultural variations in reporting side effects of medications, and/or possibly dietary factors interacting with statins.

Many factors have been reported as risk factors for statin induced myopathy, such as old age, low BMI, comorbidites (such as hypothyroidism, diabetes and renal impairment), concomitant medications known to interact with the metabolism of statins, (such as Fibrate, Cyclosporin, Calcium channel blockers, and macrolide antibiotics), alcohol abuse and even large quantities of grapefruit juice are also considered independent risk factors, although epidemiological data is conflicting in regard to this or these associations [20,21]. In our study we did not find any significant association between myopathy and hypothyroidism or medications such as fibrate, allopurinol, or calcium channel blockers. Although the risk increased with age, and the presence of comorbidities and polypharmacy, none of these attained statistical significance. Alcohol as arisk factor for statin induced myopathy couldn't be assessed as almost all our subjects were non-drinker or denied that due to religious and cultural issues.

Although diabetes has been suggested as a possible risk factor for myopathy [22], our study showed no significant association between diabetes and the occurrence of muscular symptoms (29, 7% vs 27,8%). This is consistent with Gregory A et al. study [15], which reported the rate of myopathic events in over 30,000 subjects, classified into diabetic and non-diabetic, over a 9-year period, and showed that diabetes confers no additional myopathic risk. In regard to gender, we found that myopathy was more frequent in males than females (31, 4% vs 22, 6%). This difference was close to statistical significance (p value = 0.053), a finding that contradicts with Skiliving et al. [17] which showed that women had a higher frequency of myopathy than men (17% vs 12%).

Statin-induced myopathy is considered to be dose and type dependent [8]. Our results showed an association between dose of statin and occurrence of myopathy irrespective of the statin used. The most frequently used statin in our study was atorvastatin (53.3%) followed by Rosuvastatin (23.0%), Simvastatin (19.8%), and Fluvastatin XL (3.0%). The lowest myopathy (8%) was observed with Fluvastatin XL which is consistent with the PRIMO study [9].

The highest incidence of myopathy in our study was observed with simvastatin 40 mg (50%). This finding is consistent with the PRIMO study [9], in which the highest risk of muscular symptoms was observed with simvastatin therapy, though, again, at a lower rate (18%) than ours.

The risk of muscular symptoms for atorvastatin therapy was around 15% in the PRIMO study without mentioning the rates for different doses. In our study, rates of myopathy were dose-dependent: the higher the dose, the higher the rate of myopathy: 12,5% with atorvastatin 10

mg, 21,2% with atorvastatin 20 mg, and 28.4% with atorvastatin 40 mg.

Rosuvastatin was the second most common statin used in our study (23%) after atorvastatin, and a dose of Rosuvastatin 10 mg carried the lowest risk of myopathy after Fluvastatin XL. Myopathy after Rosuvastatin was also dose dependent: 10.8% for a dose of 10 mg climbing up to 14.6% for a dose of 20 mg. According to James Shepherd et al. who evaluated Rosuvastatin in over 16,000 patients, myopathy was observed in 5.1% [23].

7. Limitations

The vast majority of the study subjects were taking atorvastatin and simvastatin, due to the high cost of other types of statins; accordingly, we could not compare the rate of muscular symptoms associated with different kinds and doses of statins. Similarly, we could not analyze some factors suggested to increase myopathy such as medications like cyclosporine and amiodarone, as they were infrequently prescribed. . Another factor that we couldn't analyze, was alcohol, as almost all our subjects were non-drinkers.

8. Conclusion

Muscular adverse reactions secondary to statin therapy are relatively common, and probably more common than previously reported in previous studies. To better, understand the mechanism and the exact relationship between Old age, comorbidity, and polypharmacy and the risk of myopathy a large cohort studies are still needed.

Finally, our study showed that treating patients with statins associated with a lower risk of myopathy, such as Fluvastatin and Rosuvastatin, may increase compliance with these medications.

Ethical approval

An informed consent was obtained from the recruited patients. All procedures performed in this study involving human participants were reviewed and ethically approved by the Institutional Review Board (IRB) and research and ethics committee at NCDEG, Amman, Jordan. This study was conducted following the 1975 Helsinki declaration, as revised in 2008 and its later amendments or comparable ethical standards.

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Author contributions

Waddah Abed:wrote, supervised and edited the manuscript.

Mousa Abujbara: helped in developing the idea and setting the protocol and reviewed the manuscript.

Anwar Batieha: perform the statistical analysis and reviewed the manuscript.

Kamel Ajlouni: was the guarantor of this work and reviewed the manuscript.

All authors equally contributed to the study concept or design, data searching, data analysis or interpretation, writing the paper.

Registration of research studies

1. Name of the registry: Statin Induced Myopathy Among Patients Attending the National Center for Diabetes, Endocrinology and Genetics.

2. Unique Identifying number or registration ID: 7406.

3. Hyperlink to your specific registration (must be publicly accessible and will be checked):
https://www.researchregistry.com/browse-the-registry#home/

Guarantor

Prof. Kamel Ajlouni.

Consent

An informed consent was obtained from the recruited patients.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103304.

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