Effect of Atorvastatin in the Occurrence of Myotoxicity Among Iraqi Patients Attending Imam Hussain Medical City in Kerbala Province

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Abstract

HMG-co A reductase inhibitor (statins) are effective drugs in cholesterol lowering with clinically significant beneficial effects when used for cardiovascular disease prevention, the leading cause of mortality worldwide. Myotoxicity associated with statin therapy are the most common adverse effect. The aim of the study is to investigate the prevalence of myotoxicity in Iraqi patients who are visiting Imam Hussain Medical City in Kerbala province and are taking atorvastatin 40 mg medication. Cross sectional study with a total of 150 participants, both male and female, ranging in age from 28 to 65 years old and receiving daily oral doses of 40 mg of atorvastatin as monotherapy for hyperlipidemia for at least one month were involved in the study. The data was collected from participants as well as from medical record and the prevalence of myotoxicity was determined by the symptoms of the participants as well as from biochemical analysis of serum creatine kinas level. The data was analyzed by using SPSS version 24. The results showed that the total prevalence of statin-related myotoxicity was 44% and only 31.3% of them reported muscular discomfort with and without creatine kinase elevation, whereas only 12.7% reported creatine kinase elevation without muscle pain. This study conclude that males are at a greater risk of developing statin-related myotoxicity ($p<0.05$) than females are, while as no significant association was found between old age, duration of treatment, smoking and body mass index, and statin related myotoxicity.

Keywords: Myotoxicity, Atorvastatin, Iraqi patients, Creatine Kinase.

1. Introduction

HMG-co A reductase inhibitor (statins) are effective drugs in cholesterol lowering with clinically significant beneficial effects when used for cardiovascular disease prevention (1,2), the leading cause of mortality worldwide (3). Myotoxicity associated with statin therapy are the most common adverse effect. Myotoxicity is a dose-dependent side effect of statins that can force patients to stop taking them(4). Indeed, the risk of muscular effects associated with statin usage has garnered the most attention since the unexpected case of cerivastatin when taken off the market on August 9, 2001, after 52 people died from rhabdomyolysis (5,6). Statin related myotoxicity (SRM) symptoms might appear after 4–6 weeks although they might also appear after several years of therapy (7). In addition, a number of predisposing risk factors that increase the likelihood of statin-induced skeletal muscle side effects have been identified. These include advanced age (>75), low body mass index, kidney or liver disease and untreated hypothyroidism, major surgery or trauma, alcohol consumption, vigorous exercise and genetic polymorphism of cytochrome p 450 isoenzymes or drug transporters (8).

Several muscular symptoms are observed such as cramps, fatigue, tenderness, pain, stiffness, and heaviness. The most frequent symptoms are those involving the legs (calf muscles, thighs), however back, neck, shoulder, and more generalized muscular problems have also been reported(9–11). Approximately 40% SRM patients report a probable trigger, most typically extraordinary physical effort or the start of a new treatment. Muscle pains occur intermittently in three-quarters of SRM patients and continuously in one-quarter (12).

The absence of established terminology and phenotypic definitions has, to some extent, impeded research in statin related myotoxicity. Previously in 2002, the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute (ACC/AHA/NHLBI) developed terminology used to categorize statin-related muscle adverse effects including myalgia, asymptomatic increases in creatine kinase (CK), myositis, and rhabdomyolysis (13). Symptoms and/or biochemical abnormalities commonly begin to manifest early after the start of therapy, disappear after stopping it, and return days to weeks later after restarting the statin (14,15). Creatine kinase (CK), a muscle injury biomarker, is routinely used to identify and assess the severity of skeletal muscle damage. However, in symptomatic patients using statins, CK values are usually normal, but in asymptomatic patients, CK value may be

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elevated (16). Due to the lack of additional specialized laboratory tests, CK is currently employed in the assessment of SRM even though it is a non-sensitive biomarker for statin-induced myopathy (17).

A worldwide expert workshop on statin-related myotoxicity was convened in December 2013 to provide more complete definitions and recognition criteria. Experts adjusted ACC/AHA/NHLBI standards and produced a numerical categorization (SRM0 to SRM6) to standardize SRM severity based on a specified algorithm. This classification described the clinical manifestations with and without CK elevation and/or muscle biopsies (18), (table 1).

To date, the mechanisms behind statin-related myotoxicity, which are tissue-specific that affecting only skeletal muscle and not cardiac or smooth muscle, are unknown (19). SRM is thought to be caused by statin buildup in the skeletal muscle in relation to risk factors (age, genetics, ethnicity, gender) (20,21). Furthermore, certain statins' physicochemical characteristics enhance their accumulation in extrahepatic tissues. It is a prevalent assumption that lipophilic statins, such as atorvastatin, might exacerbate myotoxicity because, in contrast to hydrophilic ones, they can diffuse non-selectively through the cell membranes of extra-hepatic tissues (22–24). Several mechanisms lead to statin related myotoxicity have been proposed among them impairing calcium signaling(25), induction proteolysis and apoptosis (26,27), decreased protein prenylation (28,29), oxidative stress (30), decreased coenzyme Q10 concentration (31) and When statins' systemic concentration is high enough, they can suppress cholesterol synthesis not just in the liver but also in other tissues including skeletal muscle (32). As a result, reduced cholesterol availability alters cell membrane fluidity and lipid raft integrity, making cells more susceptible to lysis (33,34). Furthermore, because ion channels and transporters are embedded within the membrane, changing the structure of the skeletal cell membrane may disrupt ion conductance and reduce muscle membrane excitability (35).

The aim of the study is to investigate the prevalence of myotoxicity in Iraqi patients who are visiting imam Hussain Medical City in Kerbala province and are taking Atorvastatin 40 mg medication.

Table 1: Classification of statin-related myotoxicity phenotypes (18).

SRM Classification	Phenotype	Incidence	Definition
SRM 0	Elevation of CK <4x ULN	1.5-26%	no muscle symptoms
SRM 1	Tolerable myalgia	.3-33%	Muscle symptoms without CK elevation
SRM 2	Intolerable myalgia	.2-2/1000 patients-years	Muscle symptoms, CK elevation <4x ULN, complete resolution on de-challenge
SRM 3	Myopathy	5/100,000 patients-years	Muscle symptoms, CK elevation >4x ULN <10x ULN, complete resolution on de-challenge
SRM 4	Severe myopathy	.11%	Muscle symptoms, CK elevation >10x ULN <50x ULN, complete resolution on de-challenge
SRM 5	Rhabdomyolysis	.1-8.4/100,000 patients-years	Muscle symptoms, CK elevation >10x ULN or <50x ULN, with evidence of renal impairment
SRM 6	Autoimmune-mediating necrotizing myositis	~2/million per year	HMGCR antibody, HMGCR expression in muscle biopsy and incomplete resolution on de-challenge

SRM: statin related myotoxicity, C.K: creatine kinase, ULN: upper limit of normal, HMGCR: 3-hydroxy-3-methylglytaryl-coenzyme A reductase.

2. Method

Study participant and overall design

Cross-sectional observational study was carried out in Imam Al-Hussein Medical City in Kerbala between November 2021 and April 2022. The Scientific and Ethical Committee of Pharmacy College/Kerbala University accepted the study's protocol, and each participant signed a consent form after being informed of the nature and purpose of the study. A total of 150 participants, both male and female, ranging in age from 28 to 65 years old and receiving daily oral doses of 40 mg of atorvastatin as monotherapy for hyperlipidemia for at least one month were involved in the study. For the purpose of classifying myotoxicity, we adapted Alfirevic et al., 2014 classification system to define statin related myotoxicity phenotypes (table 1).

Exclusion criteria for this study include patients with untreated hypothyroidism or hyperthyroidism, age >65, severe renal, hepatic, or cardiac dysfunction, recent surgery or trauma, or using drugs known to interact with atorvastatin (such as fibrates, nicotinic acid, niacin).

Blood samples were collected from patients after an overnight fast and kept in a gel tube for serum isolation for hormonal and biochemical analyses. Tests were performed on each participant to determine their lipid profile (total cholesterol, triglycerides, low density lipoprotein and high-density lipoprotein), serum creatinine, creatine kinase (C.K) and thyroid stimulating hormone levels.

Data collection

At the time of blood sample collection, patients were asked if they were taking any other drugs that could interfere with the metabolism of atorvastatin. The following data was obtained from the medical records of patients who gave their informed consent as well as directly from the patients themselves: age, weight, height, education level, type of myopathy, smoking status, duration of treatment, any adverse effects caused by the drug, other diseases, and any additional drugs taken.

Statistical analysis

The data of the present study was entered and analyzed through the Statistical Package for the Social Sciences (SPSS version 24). The data were presented as frequencies and percentages or mean and standard deviation in appropriate tables and graphs. Chi square test, Fisher's exact test, ANOVA test, T test and post hoc analysis were used where is appropriate to find out the possible association between the related variables of the current study. Statistical association considered significant when p value equal or less than 0.05.

3. Results

The ages of the 150 participants involved in the study ranged from 28 to 65 years, with a mean age of 50.9±9.2 years. The ratio of female to male was 1.20:1. More than two-thirds of the study's participants reported using atorvastatin for at least one year. Less than one-third of the study's participants (31.3%) reported experiencing muscle pain and the overall incidence of statin related myotoxicity was 44%. According to Alfirevic et al., 2014 classification system, only the first three myotoxicity phenotypes (SRM 0, SRM 1, and SRM 2) are identified in the study participants, as shown in table 2, and the mean difference of biochemical parameters of the included participants is shown in table 3.

Table 2: Socio-demographic and some related characteristics of the included participants.

Characteristics Categories		Total=150 No. (%)
Age (in years)	mean ±SD	50.9±9.2
	Range	28- 65
Age groups (years)	< 40	22 (14.7)
	40- 50	49 (32.7)
	51-60	59 (39.3)
	>60	20 (13.3)
Gender	Female	81 (54)
	Male	69 (46)
BMI	Normal weight	42 (28)
	Overweight	70 (46.7)
	Obese	38 (25.3)
Duration of treatment (months)	1-11	44 (29.3)
	12-23	41 (27.3)
	24-36	40 (26.7)
	>36	25 (16.7)
Smoking	Yes	41 (27.3)
	No	109 (72.7)
Diabetics	Yes	50 (33.3)
	No	100 (66.6)
Muscle pain	Yes	47 (31.3)
	No	103 (68.7)
SRM	SRM0	19 (12.7)
	SRM1	29 (19.3)
	SRM2	18 (12)
	Normal	84 (56)

BMI: body mass index, SD: standard deviation

Table 3: Mean difference of biochemical parameters of the included participants.

Variables	Mean	Normal range	SD	Minimum	Maximum
TSH	2.99	(0.27-5) mlU/L	11.27	0.01	137
Cholesterol	164.88	(50-200) mg/dL	50.06	52	293
TG	164.29	(35-160) mg/dL	92.66	27	621
LDL	90.94	(0-140) mg/dL	40.18	23	238
HDL	40.92	(35-65) mg/dL	11.23	18	75
SCr	0.84	(0.3-1.1) mg/dL	0.48	0.27	4.57
CK	145.75	(24-170) U/L	81.44	41	521

TSH: thyroid stimulating hormone, TG: triglycerides, LDL: low density lipoprotein, HDL: high-density lipoprotein, SCr: serum creatinine, C.K: creatine kinase

According to the analysis of the data, mean difference of biochemical parameters in relation to duration of treatment with atorvastatin was statistically significant only in regard to triglyceride ($p<0.05$) as shown in table 4.

Table 4: Association of mean biochemical parameters and duration of treatment.

Variables	Duration of treatment (months)								P value
	<12		12-23		24-36		>36		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
TSH	2.68	4.07	1.88	0.91	5.13	21.41	1.97	1.42	0.562
Chol	171.73	45.08	165.43	54.94	157.40	52.57	163.88	47.07	0.634
TG	186.86	115.85	142.17	54.71	145.45	82.58	190.96	100.43	0.032*
LDL	95.05	31.72	97.32	49.54	86.56	41.78	80.26	32.29	0.293
HDL	41.37	8.055	39.36	10.77	41.05	13.51	42.48	13.06	0.723
SCr	0.767	0.37	0.85	0.63	0.88	0.54	0.91	0.24	0.622
CK	145.61	96.02	136.27	52.06	145.30	89.88	162.24	81.07	0.668

TSH: thyroid stimulating hormone, TG: triglycerides, LDL: low density lipoprotein, HDL: high-density lipoprotein, SCr: serum creatinine, C.K: creatine kinase, SD: standard deviation.

4. Discussion

Statins (including atorvastatin) are generally well-tolerated and safe (36). Additionally, the benefits of lowering cholesterol and other pleiotropic effects outweigh the drawbacks of atorvastatin (37). Nevertheless, satin-related myotoxicity sometimes compels patients to discontinue treatment (4). SRM are reported by 10% to 33% of people taking statins. An online survey of former statin users revealed that 60% had SRM and 62% had discontinued statin therapy due to side effects (38).

The lack of agreement in the definition of SRM makes exact assessment of their real incidence difficult (39). Furthermore, the risk of statin myopathy in clinical trials (1.5-5%) is much lower than in observational studies (10-33%) (40).

According to our findings, the total prevalence of statin-related myotoxicity was 44% which agree with (41,42). Only 31.3% of them reported muscular discomfort without and with creatine kinase (C.K) elevation (SRM1 and SRM2), whereas only 12.7% reported C.K elevation without muscle pain. This study backs up prior studies that statins induce myotoxicity. The unusually high prevalence of SRM identified in our population may suggest to the relevance of genetic factors, cultural differences in reporting drug side effects, and/or potential interactions between dietary factors and statins.

Aging (>75 years) is one of many predisposing risk factors that may increase the likelihood risk of skeletal muscle side effects with statin (8). Sarcopenia, or muscular mass loss, has been linked to aging. This loss of muscle tissue occurs around the age of 50, but gets more pronounced after the age of 65. Muscular mass loss in the elderly leads to decreased muscle function (43). As a result of aging process, SRM may be more severe in the elderly population who takes statins to treat cardiovascular disease (44). This study deviates from previous studies, which found no association between age groups and SRM, while agreeing with (45). Despite the lack of statistical significance, there is a modest increase in SRM with increasing patient age. Statin-related myotoxicity was found in 36.4%, 36.6%, and 47% of participants aged <40, 40-50, and 51-60 years respectively. It is remarkable that SRM affects approximately 60% of participants over the age of 60, which is a higher percentage than the rest of the age groups. Because our study was limited to individuals under the age of 65 and the effect of statins on muscle becomes more pronounced after the age of 65, and, we were unable to accurately determine the effect of statins on the elderly.

In addition to age, this study also shows that there was no association between the patient's BMI and SRM which concur with (46).

The gender distribution was 54% female and 46% male, resulting in a female to male ratio of 1.2:1. Our data showed that males had a significantly higher proportion of SRM than females ($p<0.05$), which contradicts the findings of Skiliving et al. (47), who found that women had a higher frequency of SRM than men and matched with(48). Interestingly, SRM are more common in physically active people (49).This finding may have been influenced, in part, by the fact that male engage in greater physical activity than female do, making them more susceptible to SRM.

In this study, 150 patients had their lipid profile, thyroid stimulating hormone (TSH), serum creatinine, and creatine kinase (C.K) levels tested.

TSH was assessed to remove patients at risk of hyperthyroid or hypothyroid myopathy, separating patients with non-pharmacological muscular symptoms from those with true SRM.

Due to the lack of additional specialized laboratory tests, CK is currently employed in predicting the degree of SRM even though it is a non-sensitive biomarker for statin-related myotoxicity (17). According to our data, when compare patients who have muscular pain to those who do not have any muscle pain, there was a significant increase in the levels of C.K($P<0.0001$), indicating the role of C.K in predicting the severity of SRM. Among the mechanisms of creatine kinase (CK) elevation in response to statins are increased muscular membrane fragility caused by decreased cholesterol content, suppression of isoprenoid formation (a critical step in the biosynthesis of membrane proteins), and ubiquinone depletion resulting in mitochondrial dysfunction (50).

A systematic review of 35 randomized, placebo-controlled studies of the six FDA-approved statins found no significant differences in CK elevations between statin-treated and placebo patients (51). The previous study is consistent with our study as average of creatine kinase show no significant increase with duration of treatment groups as shown in table 4. Parker et al. (2013), on the other hand, found that atorvastatin caused a significant increase in creatine kinase average($P<0.0001$) (52).

Atorvastatin has been found to reduce cholesterol levels effectively (5). The same was confirmed in our study (table 4), where the mean of cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels after <12, 12-36 and >36 months of atorvastatin 40mg treatment are within normal range, indicating the role of atorvastatin in correcting cholesterol levels in patients with hyperlipidemia.

However, the results were not the same for triglycerides (TG), our data show that the mean TG level significantly higher when duration of treatment <12 months or >36 months compared to duration of treatment 12-36 months. In large cross-sectional observational study found that dyslipidemia is widespread among patients with T2DM in the United Kingdom and TG remain high after statin monotherapy. The main conclusion was

that Persistent hypertriglyceridemia was frequent, affecting half of those taking statins alone (53). The previous study may explain the particular increase in triglycerides since 50 patients in this study had type 2 diabetes mellitus, and more than half of them (33 patients) had hypertriglyceridemia, with the majority of those patients falling into the <12 and >36 months duration of treatment groups. In addition, our data did not take into account a baseline triglyceride value before starting treatment to estimate the extent of the triglyceride reduction.

5. Conclusion

Muscle adverse reactions as a result of treatment with atorvastatin are relatively common, and it's likely that they're far more common than was previously reported. According to the findings, males are at a greater risk of developing statin-related myopathy than females are. There is still a need for large cohort studies in order to get a better understanding of the mechanism behind statin-related myotoxicity and its exact association with risk factors such as old age, body mass index (BMI), duration of treatment, and others.

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