Endocrinology & Metabolic Syndrome
ISSN: 2161-1017

Khlief, et al., Endocrinol Metab Syndr 2015, 4:4
DOI: 10.4172/2161-1017.1000204

Research Article Open Access

Prevalence of Myopathy in Subjects on Statin Therapy Attending the National Center for Diabetes, Endocrinology and Genetics in Jordan

Yazan Khlief[1], Dana Hyassat[1], Mohammed Liswi[1], Hashem Jaddou[2] and Kamel Ajlouni[1,*]

[1]*National Center for Diabetes, Endocrinology and Genetics, Aman, Jordan*

[2]*Department of Public Health, Community Medicine, Jordan University of Science & Technology, Irbid 22110, Jordan*

Abstract

Objective: This study aims to find the prevalence and risk factors of myopathy in subjects on statin therapy.

Methods: Cross sectional study was conducted on 1046 subjects on statin therapy for dyslipidemia who were attending the National center for Diabetes, Endocrinology and Genetics [NCDEG] in Jordan between Sep. and Dec. 2012. Questionnaire was used to collect demographic data, medical history and muscular symptoms.

Results: The prevalence of muscular symptoms among subjects taking statin was 27.9%, when subjects referred their muscular symptoms to statin the prevalence drop to 16.4%. Bivariate and multivariate analyses showed significant association between muscular symptoms and hypothyroidism, taking medication or substances that are known to interact with statin treatment [Fibrates, Verapamil, Amiodarone, Warfarin, Digoxin or Grapefruit juice [>1 quart/day]], and allopurinol therapy.

Conclusions: Statin use is significantly associated with high prevalence of musculoskeletal pain [27.9%]. Although many clinicians perceive myalgia as a minor adverse effect, its clinical significance should not be underestimated, as myalgia could be a major obstacle to treatment adherence.

Keywords: Prevalence; Myopathy; Statins

Introduction

High plasma levels of total cholesterol and Low-Density Lipoprotein [LDL] are well-established risk factors for coronary heart disease [1-3]. Statins significantly lower cholesterol levels and have been shown to significantly reduce morbidity and mortality associated with heart disease [4-8]. Because statins are potentially lifesaving, their tolerability and adherence is a major concern. Generally, statins are well tolerated with minimal serious side effects [9].

Muscular side effects are recognized as the most common adverse effect associated with statin use [9-13]. The incidence of myalgia [generally defined as muscle symptoms without significant creatine kinase elevation] approximates 1-7% of statin-users in randomized clinical trials, with rates similar to placebo groups [12-14]. However, the frequency of muscle complaints reported in usual care settings appears to be higher than in clinical trials with a frequency of 9% to 22% in outpatient settings [15-18].

Since adherence on statin therapy can be limited by patients concerns about serious muscle toxicity and by more frequent but less severe side effects of muscle aches, pain, weakness and cramps, and given the more aggressive approach to lipid-lowering therapy advocated by recent treatment guidelines; an increased understanding of the nature of statin muscular side effects is of considerable importance [19].

The main objectives of this study were to assess the prevalence of statin-induced myopathy, to identify the risk factors associated with muscular symptoms and to characterize the onset, nature and management of muscular symptoms in individuals on statin therapy.

Materials and Methods

Sampling and data collection

This is a cross-sectional study which was carried out at the National Centre for Diabetes, Endocrinology and Genetics in Amman, Jordan, over a period of three months [Sep 2012 to Dec 2012]; any patient aged 40 years or more and on statin therapy, was considered eligible to be included in this study. Patients' demographic and clinical data were collected from medical records. A pre-structured questionnaire was used to collect the patients' muscular symptoms history. This included the type, dose and duration of statin used along with other concomitant medications and chronic diseases were obtained. In addition, the nature and duration of muscle symptoms [pain, fatigue, tenderness, weakness, stiffness and cramps] were included in the questionnaire. Laboratory investigations such as Creatine Kinase [CK] levels, Thyroid-Stimulating Hormone [TSH], Serum Electrolytes, Vitamin D levels, were also collected from the medical records.

The present study was approved by the National Centre for Diabetes, Endocrinology and Genetics [NCDEG] Ethics Committee. Identifying information was kept strictly confidential and the data were used only for scientific purposes by the researchers. A verbal approval was obtained from all patients who participated in the study.

Definitions of the study variables

Measurements and laboratory analysis: BMI was expressed as the quotient between weight [kg] and height squared meter [m^2]. Patients were classified according to BMI following the recommendation of the World Health Organization as adopted by the American Diabetes Association. The patients weight considered normal weight if BMI was in the range of 18.5 up to 24.9, overweight when their BMI was 25 and up to 29.9, and obesity was considered if BMI was 30 or more [20].

***Corresponding author:** Kamel Ajlouni, National Center for Diabetes, Endocrinology and Genetics, Aman 11942, Jordan, Tel: +962 6 534 7810; Fax: +962 6 535 6670; E-mail: ajlouni@ju.edu.jo

Received November 02, 2015; **Accepted** November 05, 2015; **Published** November 09, 2015

Citation: Khlief Y, Hyassat D, Liswi M, Jaddou H, Ajlouni K (2015) Prevalence of Myopathy in Subjects on Statin Therapy Attending the National Center for Diabetes, Endocrinology and Genetics in Jordan. Endocrinol Metab Syndr 4: 204. doi:10.4172/2161-1017.1000204

Smoking was classified into three categories; current smoker defined as a person who smokes cigarettes daily or occasionally. Past-smoker: a person who was formerly a daily or occasional smoker, but currently does not smoke at all. Nonsmoker: a person who has never smoked before or has smoked very little in the past, and this definition was according to WHO guidelines 1998 [21].

Exercise considered present if at least 150 min/week of moderate-intensity aerobic physical activity, spread over at least 3 days/week with no more than two consecutive days without exercise [20].

Diabetes mellitus was diagnosed if the patient had a fasting plasma glucose ≥126 mg/dl [7.0 mmol/l] in two occasions or if the patient had a random plasma glucose ≥200 mg/dl [11.1mmol/l] in the presence of classical symptoms of hyperglycemia, or if he had HbA1C ≥6.5%. Moreover, Diabetes was considered to be controlled if the patient had HbA1C <7.0% [20].

High blood pressure was defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg or if the patient was already on antihypertensive drugs [20].

Metabolic abnormalities were defined according to the American Diabetes Association 2011 [18] as follows: Total serum cholesterol of ≥200 mg/dl, Serum LDL of ≥100 mg/dl, Serum triglyceride of ≥150 mg/dl, Serum HDL ≤40 mg/dl in men, and ≤50 mg/dl in women, or if the patient was already on anti-dyslipidemic agents [20].

Definition of myopathy and related terms as described by American College of Cardiology/American Heart Association/National Heart Lung Blood Institute clinical advisory [12]: Myopathy: Any disease of neuromuscular origin in which abnormal muscle fiber gives the symptoms muscle weakness, muscle cramps, stiffness, and spasm. This abnormality can be inherited or acquired. Myalgia: Muscle ache or weakness without creatinine kinase elevation. Myositis: Muscle symptoms with increased creatinine kinase levels. Rhabdomyolysis: Muscle symptoms associated with marked creatinine kinase elevations, typically substantially more than 10 times the upper limit of normal.

Statin induce myopathy was defined in this study as any muscular pain reported by the patients after starting the statins therapy, or those who already suffer from muscular pain before the statin treatment but their muscular pain became more severe after the treatment, with or without creatinine kinase elevation.

Medication or substances that were known to interact with statin treatment include: Fibrates, Verapamil, Amiodarone, Warfarin, Digoxin or Grapefruit juice [>1 quart/day] [22].

Level of disruption of daily activity was classified into 4 levels; minor disruption if there is mild muscular pain and no limitation for any physical activity, Interferes with major exertion if heavy physical activity is limited by muscular pain, interferes with moderate exertion if moderate physical activity is limited by muscular pain, and major disruption if muscular pain prevent patient from any physical activity [16].

Statistical Analysis

Data were entered and analyzed using the Statistical Package for Social Science [SPSS version 17]. The prevalence of statin-induced myopathy was obtained, overall and by 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. Multivariate logistic regression was used to assess the independent effect of a given variable after adjusting for potential confounders. A P-value of ≤0.05 was considered statistically significant.

Results

One thousand forty-sixth subjects agreed to participate in this study; 577 [55.2%] were females and 469[44.8%] were males. The mean age of our study participants was 58.9 [±8.8] with mean BMI of 31.6 [±5.5]. Ninety two percent of our sample had type two diabetes, 75% had hypertension, 13% had coronary artery disease, 11% had hypothyroidism, and 4% had osteoporosis (Table 1).

Eighty two percent of our study subjects reported not to be engaging in regular physical activity (Table 1). Most of our study participants [76%] were on Atorvastatin and the most prescribed dose was 20 mg [79% of our study sample] (Table 2).

Twenty eight percent of the whole sample had reported muscular pain, and among those who reported muscular pain 59% had attributed their pain to statin use. Onset of muscle pain in 51% of them was reported at the period between 4 and 24 months, 31% at the period after 24 months, and only 19% of them had their statin related muscular pain in the first 4 months. No triggering factors [physical activity, cold and resting] for statin induced muscular pain was reported in 63% of patients (Table 3).

The most common sites of pain were thighs, calves and arms 39.5%, 23.4% and 24.2%, respectively. Common types of pain were stiffness [37.8%], cramps [23.8%] and weakness [23.3%]. However 81% of those having statin-induced muscular pain had reported that this pain had minor effect on their daily activities, as 75% of all those who had statin-induced muscular pain did not need any action to overcome their pain: 13% took simple analgesics while continuing their statin treatment, and 7% needed to discontinue the statin therapy (Table 3).

Bivariate Analysis

On bivariate analysis, statin induced myopathy was significantly associated with hypothyroidism [p value .034], taking medication or substances that are known to interact with statin treatment [Fibrates, Verapamil, Amiodarone, Warfarin, Digoxin or Grapefruit juice [>1 quart/day]] [p value .050] and Allopurinol [p value .047]. However, age, gender, BMI, smoking, diabetes mellitus, vitamin D3 status, and the laboratory results of creatinine kinase were not significantly associated with statin induced myopathy (Table 4).

Multivariate Analysis

On logistic multivariate analysis, the study variables that remained significantly associated with statin-induced myopathy were hypothyroidism, taking medications that were known to interact with statin therapy and Allopurinol use.

Patients with hypothyroidism were 1.6 times more likely to develop statin-induced myopathy in comparison to those who had no hypothyroidism, after controlling for other variables. Patients taking medication or substances that are known to interact with statin treatment [Fibrates, Verapamil, Amiodarone, Warfarin, Digoxin or Grapefruit juice [>1 quart/day]] were 1.5 times more prone to have statin induced than patients who were not on the above mentioned medication, after controlling for other variables. On the other hand, patients who were taking Allopurinol treatment for hyperuriceamia were 2 times more likely to have statin induced myopathy than patients who were not taking Allopurinol, after controlling for other variables (Table 5).

Characteristics	N	%
Gender		
Male	469	44.8
Female	577	55.2
Age(mean ± SD) (58.91 ± 8.8)		
40-49	158	15.1
50-59	403	38.5
60-69	335	32.0
≥70	150	14.3
BMI (mean ± SD) (31.6 ± 5.5)		
18.5-24.99	101	9.7
25-29.99	355	34.1
30-39.99	506	48.6
≥40	80	7.7
Smoking		
Current smoker	180	17.2
Past-smoker	181	17.3
Nonsmoker	685	65.5
Exercise		
Yes	196	18.5
No	852	81.5
Co-morbidity		
Diabetes Mellitus	957	91.5
Hypertension	788	75.3
Coronary Artery Diseases	136	13
Hypothyroidism	118	11.3
Osteoporosis	40	3.8

Table 1: Socio-demographic characteristics of study participants (N=1046).

Item	Category	Number (%)
Type of statin	Simvastatin	197 (18.8)
	Atorvastatin	793 (75.8)
	Rosuvastatin	17 (1.6)
	Fluvastatin	9 (0.9)
	Pravastatin	30 (2.9)
Statin daily dosage in mg	10	152 (14.5)
	20	824 (78.8)
	40	64 (6.1)
	80	6 (0.6)
Duration of statin treatment	≤ 36 months	538 (51.4)
	> 36 months	508 (48.6)

Table 2: Characteristics of statin treatment.

Discussion

The rate of occurrence of muscular symptoms in patients receiving statins was 28% considerably higher than the 1-5% reported by randomized clinical trials [12-14]. It is even higher than the rate reported by the PRIMO study in which muscular symptoms were reported by 11% of statin users [16]. In Jordan EL-SALEM et al in his study had also demonstrated a high prevalence of muscular symptoms [21%] among patients using statins [23].

Item	Category	Number (%)
Onset of pain	≤3 months	32 (18.6)
	4-24 months	87 (50.6)
	>24 months	53 (30.8)
Type of pain	Weakness	40 (23.3)
	Heaviness	19 (11.0)
	Loss of strength	7 (4.1)
	Stiffness	65 (37.8)
	Cramp	41 (23.8)
Localization	Generalized	48 (29.9)
	Localized	124 (72.1)
Sites of localized pain	Thighs	49 (39.5)
	Calves	29 (23.4)
	Trunk	3 (2.4)
	Arms	30 (24.2)
	Forearms	3 (2.4)
	Shoulders	8 (6.5)
	No predominance	2 (1.6)
Continuity of pain	Continuous	20 (11.6)
	Hours	73 (42.4)
	Minutes	79 (45.9)
Triggering factors	No	108 (62.8)
	Physical activity	46 (26.7)
	Resting	6 (3.5)
	Cold	12 (7.0)
Level of disruption	Minor effect	139 (80.8)
	Interfere with major exertion	14 (8.1)
	Interfere with minor exertion	16 (9.3)
	Major effect	3 (1.7)
Action was taken to manage the statin induced myopathy	No action	129 (75.0)
	Switch	8 (4.7)
	Discontinue	12 (7.0)
	Reduce	1 (0.6)
	Analgesic	22 (12.8)
Improved after action	Yes	30 (69.8)
	No	13 (30.2)

Table 3: Time to onset, characteristics, localization, continuity, triggering factors, and impact on daily activities of statin- induced muscle pain and the actions were taken to manage the statin induced myopathy.

Age, gender, Body Mass Index [BMI] and smoking were not identified as risk factors for myopathy by bivariate analysis in our study. Although there are, some studies that showed that elderly are at increased risk for statin induced myopathy [24,25]. In fact, in one of these studies, diabetic patients aged 65years or older prescribed

Variable	Number of patients with statin induced myopathy (%)	P-value
Age		
40 - 49 years	30 (17.4)	0.730
50 - 59 years	68 (39.5)	
60 – 69 years	51 (29.7)	
≥ 70 years	23 (13.4)	
Gender		
Male	72(41.9)	0.403
Female	100(58.1)	
BMI		
18.5-24.99	18(10.5)	0.248
25-29.99	67(39.2)	
30-39.99	71(41.5)	
≥40	15(8.8)	
Smoking		
Current smoker	31 (18)	0.702
Past-smoker	26 (15.1)	
Nonsmoker	115 (66.9)	
Diabetes mellitus		
Yes	154 (89.5)	0.298
No	18 (10.5)	
Hypothyroidism		
Yes	28(16.3)	0.034
No	144(83.7)	
Allopurinol		
Yes	13(7.6)	0.047
No	159(92.4)	
Taking any medication that might interact with statin		
Yes	67 (39)	0.050
No	105 (61)	
Vitamin D3 status (ng/ml)		
< 20	46 (29.9)	0.941
20 – 30	36 (23.4)	
> 30	72 (46.8)	

CKP		
Normal	77 (90.6)	0.584
Abnormal	8 (9.4)	

Table 4: Bivariate analysis of factors associated with statin induced myopathy

Variable	OR	P-value
Age		
40 - 49 years	1	
50 - 59 years	0.81	0.383
60 – 69 years	0.72	0.203
≥70 years	0.71	0.263
Gender		
Male	1	0.186
Female	1.28	
BMI		
<25	1.25	
25-29.99	1.26	0.580
30-39.99	0.81	0.490
≥40	1	0.506
Hypothyroidism		
Yes	1.63	0.043
No	1	
Allopurinol		
Yes	2.18	0.026
No	1	
Taking any medication that might interact with statin		
Yes	1.46	.032
No	1	

Table 5: Multivariate analysis of factors associated with statin induced myopathy.

lipid lowering agents had more than five times risk for hospitalization due to rhabdomyolysis than younger counterparts and this might be due to existence of multiple risk factors for myopathy such as the use of concomitant medication, the presence of some disorders such as diabetes mellitus and small body frame [frailty], age related decline in renal and hepatic function, which in turn increase the risk for muscle complain in the elderly due to the increased levels of statin therapy, thus statin –associated myopathy could negatively affect elderly patients ability to perform daily activity and predisposing them to more hospitalization, nursing home admission and increased mortality among them.

Inconsistent with our findings, physical activity may exacerbate muscle complaints associated with statins in different studies [24,25]. In PRIMO study for example, 20% of patients with muscle complaints had reported recent physical activity [16]. Thompson et al in another study had reported that CK elevation was observed in 62% and 72% of sedentary individuals following downhill treadmill exercise [at 24 and 48 hours, respectively] [26]. Moreover, the observation that, smokers were less likely to experience muscle pain could be by the fact that smokers are usually less physically active and they could not tolerate exercise for long period. On the other hand, physicians should be aware that many CK elevations during statin treatment are exercise related and they should evaluate this possibility before permanently stopping statin therapy.

One of the most common considerations for physicians prescribing statin treatment is polypharmacy because patients with dyslipidemia are more likely to be on multiple other medications for cardiovascular disease [10]. Our study showed that concomitant use of statins with Allopurinol and other medication increases the risk of developing statin- induced myopathy by 2.18 for Allopurinol and 1.46 for other medication, respectively. It is notable that although concomitant medication per se was not associated with a significantly higher risk of muscular symptoms in the PRIMO study [OR 1.15; 95%CI 0.48-1.34; p=0.081], starting a new medication was identified as a triggering factor for muscular symptoms by 30%of patients who reported potential factors [16].

Although the risk for statin-induced muscle dysfunction increases in patients prescribed multiple medications, it is difficult to predict the probability of drug-interaction-related myopathy due to the variability of patients' sensitivity to statin levels.

The most common medication for statin drug interaction involves the cytochrome p-450 system. Approximately 40%of all drugs [including most statins] are metabolized by the cytochrome p-450 system. The choice of statin in various patient groups requires consideration of other factors, including statin potency and renal clearance, keeping in mind that agent not requiring CYP3A4 metabolism including Pravostatin, Fluvastatin and Rosuvastatin [CYP2C9] have theoretical advantages in patients receiving multiple drug treatment [24,25].

This study was one of the few studies done in Jordan to assess the prevalence and associated risk factors for statin-induced myopathy.

Limitations

The vast majority of the study patients were taking Atorvastatin so we could not compare the rate of occurrence of muscular symptoms with different kinds and doses of statins. It would have added more value to our findings had neurophysiologic testing with electromyography.

Conclusions

Statin use is significantly associated with high prevalence of musculoskeletal pain [27.9%]. Although many clinicians perceive

myalgia as a minor, adverse effect but it could be a major obstacle to treatment adherence.

Numerous approaches to the statin-intolerant patients have been suggested, however, it is important to rule out secondary causes of myopathy [physical activity, hypothyroidism, drug interactions].

The clinician can reduce the incidence of statin-myopathy by assessing each patient for the most common risk factors for statin myopathy and adjust the dose of statin or change it to another statin for those at risk. Prospective studies on stratified large cohorts of patients with variable demographic and disease characteristics are still needed to better understand the prevalence, risk factors, and natural history of statin-induced myopathy.

References

1. (1984) The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA: the journal of the American Medical Association 251(3): 365-74.
2. LaRosa JC, Hunninghake D, Bush D, Criqui MH, Getz GS, et al. (1990) The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. The Task Force on Cholesterol Issues, American Heart Association. Circulation 81: 1721-33.
3. (1984) The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA: the journal of the American Medical Association 251(3): 351-64.
4. [No authors listed] (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) Lancet 344: 1383-1389.
5. [No authors listed] (1994) Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS) Lancet 344: 633-638.
6. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, et al. (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. The New England journal of medicine, 333: 1301-1307.
7. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, et al. (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. The New England journal of medicine 335(14): 1001-9.
8. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, et al. (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 364(9435): 685-96.
9. McKenney JM, Davidson MH, Jacobson TA, Guyton JR (2006) National Lipid Association Statin Safety Assessment Task F. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. The American journal of cardiology. 97(8A): 89C-94C.
10. Nichols GA, Koro CE (2007) Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. Clinical therapeutics 29(8): 1761-70.
11. Thompson PD, Clarkson PM, Rosenson RS; National Lipid Association Statin Safety Task Force Muscle Safety Expert Panel (2006) An assessment of statin safety by muscle experts. Am J Cardiol 97: 69C-76C.
12. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, et al. (2002) ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Circulation. 106(8): 1024-8.
13. Ucar M, Mjörndal T, Dahlqvist R (2000) HMG-CoA reductase inhibitors and myotoxicity. Drug Saf 22: 441-457.
14. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, et al. (2006) Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation 114: 2788-2797.
15. Sauvage Nolting PR, Buirma RJ, Hutten BA, Kastelein JJ, Dutch Ex PIG. Two-year efficacy and safety of simvastatin 80 mg in familial hypercholesterolemia (the Examination of Probands and Relatives in Statin Studies with Familial Hypercholesterolemia [ExPRESS FH]). The American journal of cardiology 90(2): 181-4.
16. Franc S, Dejager S, Bruckert E, Chauvenet M, Giral P, et al. (2003) A comprehensive description of muscle symptoms associated with lipid-lowering drugs. Cardiovascular drugs and therapy/sponsored by the International Society of Cardiovascular Pharmacotherapy 17(5-6): 459-65.
17. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B (2005) Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovascular drugs and therapy/sponsored by the International Society of Cardiovascular Pharmacotherapy 19(6): 403-14.
18. Buettner C, Davis RB, Leveille SG, Mittleman MA, Mukamal KJ (2008) Prevalence of musculoskeletal pain and statin use. J Gen Intern Med 23: 1182-1186.
19. Harper CR, Jacobson TA (2007) The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Curr Opin Lipidol 18: 401-408.
20. American Diabetes Association (2013) Standards of medical care in diabetes--2013. Diabetes Care 36 Suppl 1: S11-66.
21. Raw M, McNeill A, West R (1998) Smoking cessation guidelines for health professionals. A guide to effective smoking cessation interventions for the health care system. Health Education Authority. Thorax 53 Suppl 5 Pt 1: S1-19.
22. Mukhtar RY, Reckless JP (2005) Statin-induced myositis: a commonly encountered or rare side effect? Curr Opin Lipidol 16: 640-647.
23. El-Salem K, Ababneh B, Rudnicki S, Malkawi A, Alrefai A, et al. (2011) Prevalence and risk factors of muscle complications secondary to statins. Muscle Nerve 44: 877-881.
24. Tomlinson SS, Mangione KK (2005) Potential adverse effects of statins on muscle. Phys Ther 85: 459-465.
25. Sathasivam S (2012) Statin induced myotoxicity. Eur J Intern Med 23: 317-324.
26. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggers J, et al. (1997) Lovastatin increases exercise-induced skeletal muscle injury. Metabolism 46: 1206-1210.