Prevalence of statin induced myopathy in Lahore, Pakistan

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Abstract: Cardiovascular diseases are considered to be the leading cause of disability and deaths in the whole world. The major cause behind this disease is the formation of lipid plagues in the form of thrombus. The statins (HMG-CoA reductase inhibitors) are used for the treatment and prevention of hyperlipidemia. Myopathy is the major side effect caused by statins. The purpose of this study was to determine the prevalence of statin induced myopathy. A cross-sectional study design was adopted using convenient random sampling technique at Punjab Institute of Cardiology, Lahore Pakistan from November 2016 to February 2017. A total of 300 male and female patients were included having age range of 40-80 years. Data was collected directly from the patients and prevalence of myalgia was determined by the symptoms of the patients. Creatine Phospho Kinase levels were obtained of those patients showing symptoms. Data was analyzed by using SPSS version 21. The results showed that 51% patients were myalgic with mean±SEM, 1.49±0.29. Myalgia was more prevalent in age range 40-50, with females 57% and males 47%. Significant relation was found between myalgia and type of statin (p=0.05), duration of use of statin (p=0.036) and dose of statin (p=0.031). The study concludes that the prevalence of myalgia was not significant but females were more prone to myalgic symptoms as compared to males. It was further concluded that myalgic symptoms were directly related to dose and duration & type of statin use.

Keywords: Myalgia, Statin, Prevalence, CPK, Myopathy, HMG-CoA.

INTRODUCTION

Cardiovascular diseases are considered to be the leading cause of disability and deaths in the whole world. The major cause being the formation of lipid plagues in the form of thrombus. The statins (HMG-CoA reductase inhibitors) have been used to treat hypercholesteremia since 1987. It was reported that statins are prescribed in over 100 million prescriptions per year (Sathasivam & lecky, 2008).These medicines act by lowering the levels of low density lipoproteins-cholesterol (LDL) that is the bad cholesterol in the blood stream. Hardening and narrowing of arteries may occur if the LDL cholesterol level is high leading to a potential threat for cardiovascular diseases (Hassanabad, 2012).

The statins lower the cholesterol level by converting HMG-CoA to mevalonate catalyzed by HMG-CoA reductase that is the rate limiting step in the de novo pathway for cholesterol synthesis (Bonetti *et al*., 2003). Apart from lipid modifying properties statins have also other beneficial effects on cardiovascular events. These properties include improvement of endothelial cell functions, reduction of smooth muscle cell proliferation and cholesterol accumulation, modification of inflammatory responses and inhibition of synthesis of non-steroidal isoprenoid compounds which are also produced from mevalonic acid (Liao *et al*., 2005).

Myopathy is the major and very serious side effect caused by statins, which is initiated by myalgia, muscle pain, fatigue, and tenderness and may lead to myopathy. In rare cases myopathy can worsen to life threatening rhabdomyolysis i.e. the dystrophy of muscles. The incidence of myopathy and rhabdomyolysis increases when statins are given in combination with other lipid lowering drugs for example gemfibrozil, niacin or other fibrates. Insomnia, nausea, diarrhea, asthenia, abdominal pain, flatulence, constipation, dyspepsia and headache are other uncommon side effects associated with statins (Schick, 2008).

Statin's-associated myopathy, with significant elevation of serum CK, is a rare but serious side effect of statins, affecting 1 in 1000 to 1 in 10, 000 people on standard statin doses. Statin's-associated muscle symptoms cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels, with a prevalence of 7–29% in registries and observational studies (Stores *et al*., 2015).

A defined mechanism responsible for the statin induced myopathy is not yet completely understood. However many theories do exist. It has been concluded by reviewing different researches that an alteration in myocyte membrane cholesterol may occur as a result of reduction in cholesterol concentration. In another aspect it was concluded that depletion of isoprenoids may occur that is responsible in controlling myofiber apoptosis. The final mechanism suggests that potential myotoxicity of statins is the result of diminution of ubiquinone or Coenzyme Q10 (CoQ10) (Marcoff *et al*., 2007).

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Khlief and his coworkers conducted a study at National Center for Diabetes, Endocrinology and Genetics in Jorden and found that 27.9% patients taking statins complained muscle problems but the percentage dropped to 16.4% when myopathy was associated with statins. They concluded that most of the myopathy pains were either associated with hypothyroidism or due to combination with other drugs that enhances the myopathy effects of statins like verapamil, fibrates, warfarin, amiodarone, digoxin or grape fruit juice and allopurinol. They further reported that myopathy is the most leading side effect of statins that occur in 27.9% of the patients (Khlief *et al*., 2015).

Law and his colleagues revealed that the patients taking Gemfibrozil along with Simvastatin, Atorvastatin or Lovastatin used to inhibit fibrates which was observed in 19% of the cases while the patients taking Azole anti-fungal or erythromycin in combination with any of the above mentioned statins used to inhibit cytochrome 3 or 4 which comprises of 60% of the cases. Most common side effect was myopathy which was 11 per 100,000 persons per year (Law *et al*., 2006).

Basu concluded that Myopathy is the most common side effect of statins and is exacerbated when statins are used in higher doses and become even worse when are taken in combination with those drugs that follow the same pathway as statins (Basu, 2002; Golomband & Evans, 2008; Staffa *et al*., 2002; Mendes *et al*.,2014). It is an estimate that over 1.5 million people per year using statins experience muscle related problems (Sathasivam & Lecky, 2008). Myopathy is the commonest side effect of statins which can be easily resolved in most of the patients within a month after the withdrawal of the treatment (Hansen *et al*., 2005).

Asians consume large amount of fats in their food so are on the highest risk to be threatened by this disease. The present study was done to assess prevalence of statin induced myopathy in Lahore Pakistan.

MATERIALS AND METHODS

A cross-sectional study design was adopted using convenient random sampling technique at Punjab Institute of Cardiology, Lahore Pakistan from November 2016 to February 2017. A total of 300 patients were included in the study. Both male and female participated between the age range of 40-80 years. Patients showing muscle problems or not showing muscle problems whether diabetic or non-diabetic and ischemic heart disease patients were included.

Patients less than 40 years and greater than 80 years were excluded from the study. Moreover Patients having any sort of cancer, periodontal disease; heart failure and migraine were not included in the study.

Data collection procedure

Data was collected from patients visiting the out-patient department of Punjab Institute of Cardiology Lahore. The patients were divided into two groups, Group A and B. Group A patients were receiving atorvastatin while group B patients were using rosuvastatin for more than one year at different doses (10mg, 20mg, 40mg). Performa's were filled with the consent of the patient in the presence of cardiologist. The demographic data (age, gender, name, phone number, living style) statin used, dose, duration, time of taking statin, presence of myalgic symptoms, PIC registration number and presence of any other disease (diabetic or non-diabetic) was collected directly from the patient and patient record file. The regimen of the patient was noted from patient's personal booklet.

Ethical considerations

The study was approved from Board of Studies, Institute of Pharmacy and Advance Studies Research Board Lahore College for Women University Lahore. Afterwards the study design/protocol and the Performa were approved by the ethical committee of PIC along with consent forms, both in English and Urdu. Furthermore, consent of patient was taken and confidentiality of information was assured.

STATISTICAL ANALYSIS

All the results were analyzed by using two softwares, SPSS version 21 and Graf pad prism 7. Descriptive statistics (mean, standard deviation, frequency, percentage was applied to summarize the data (Harriss *et al*., 2006). The results of prevalence study were analyzed by using SPSS version 21. Chi square test was applied for the comparison of qualitative data like determination of prevalence of myopathy, diabetic considerations, comparison of myopathy with gender, dose, duration, age and the most important statin.

RESULTS

Demographic characteristics of patients

Demographic data is depicted in table 1. Age ranges from 40-80 years, with mean age 55.55. In the age group 40-50, 65(56%) were males while 51(44%) were females. In age group 51-60, 61(57.54%) were males and 45(42.45%) were females. In 61-70 age group 46(69%) were males and 21(31%) were females. In 71-80 age group, 7(63.63%) were males while 4(36.36) were females.

Table 2 depicts that overall, a total of 153 (51%) were myalgic while 147 (49%) had no myalgia. Evaluation of myalgia with respect to age groups is depicted in Table-3. In age group 40-50 years, 60(51.7%) were myalgic, in 51-60 age group, 50 (47.2%) were myalgic, in 61-70 age group, 37 (55.2%) were myalgic and in 71-80 age group, 7 (63.63%) were myalgic patients.

Table 1: Demographic characteristics of patients

Age (year) groups	Gender	Frequency (%)	Total N=300
40-50	Male	65(56)	116(39)
	Female	51(44)	
51-60	Male	61(57.54)	106(35)
	Female	45(42.45)	
61-70	Male	46(69)	67(22)
	Female	21(31)	
71-80	Male	7(63.63)	11(4)
	Female	4(36.36)	

Table 2: Prevalence of myalgia

Yes	153 (51%)	Mean ± SEM =1.49±0.29
No	147 (49%)	(p=0.375)

Table-3: Evaluation of myalgia with respect to age groups

Age(years) groups	No of patients	Evaluation of myalgia	Frequency(%)
40-50	116	Myalgic	60(51.7)
		Non myalgic	56(48.3)
51-60	106	Myalgic	50(47.2)
		Non myalgic	56(52.8)
61-70	67	Myalgic	37(55.2)
		Non myalgic	30(44.8)
71-80	11	Myalgic	7(63.63)
		Non myalgic	4(36.46)

Table 4: Presence of myalgia with respect to gender and statin used

Variable	Groups	Presence of myalgia	Frequency (%)	Total	P value
Gender	Male	Yes	84(47)	179	0.086
		No	95(53)		
	Female	Yes	69(57)	121	
		No	52(43)		
Statin	Atorvastatin	Yes	126(52)	243	0.05
		No	117(48)		
	Rosuvastatin	Yes	27(47)	57	
		No	30(53)		

Table 4 depicts presence of myalgia with respect to gender and statin used. Among males, 84(47%) were myalgic while in females 69(57%) were myalgic. Among patients using atorvastatin, 126(52%) were myalgic while among patients using rosuvastatin, 27(47%) showing a significant relation with respect to statin used (p=0.05).

Presence of myalgia with respect to dose of statin is depicted in Table-5. A significant relation was found with respect to dose of statin used and presence of myalgia (p=0.031).

Presence of myalgia with respect to duration of statin is depicted in Figure-1. A significant association was observed between the duration of statin use and presence of myalgia (p=0.036).

DISCUSSION

Cardiovascular diseases are increasing day by day and their occurrence is different in different genders. In the findings of present study Ischemic heart disease was observed in 59.7% males and 40.3% females. This is in line with the findings of Fatmi and coworkers which depicted that men of higher age groups were more prone to these diseases as compared to females (Fatmi *et al.*, 2013) Statins are the drugs that perform a beneficial effect in controlling and preventing Ischemic heart disease by

Table 5: Presence of myalgia with respect to dose

Dose in mg	Presence of myalgia	Frequency (%)	Total patients	P value
5	Yes	1(100)	1	0.031
	No	0 (0)		
10	Yes	22(7.3)	55	
	No	33(11)		
20	Yes	122(51.6)	235	
	No	113(37.6)		
40	Yes	8(2.6)	9	
	No	1(0.33)		
Total	Yes	153(51)	300	
	No	147(49)		

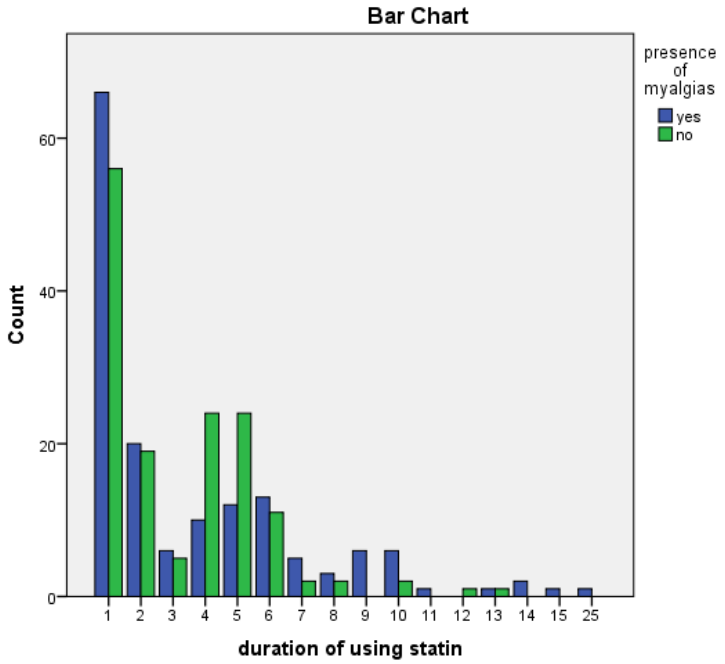

Fig. 1: Presence of myalgia with respect to duration of statin use P=0.036

lowering the lipid levels. Along with benefits all drugs are also associated with some risks and myopathy is the most common problem worldwide caused by statins (Khlief *et al*., 2015; Law *et al*., 2006; Mendes *et al*., 2014). The present study showed that 51% patients have the symptom of myalgia. Supportive evidences found from some other researchers who depicted that Asians are more prone to myalgia due to some genetic reasons such as muscular disorder or genetic variation in statin uptake proteins encoded by SLCO1B1 or the cytochrome p enzyme which alter the metabolism of statin and for that reason increases the risk of myopathy (Feng *et al*., 2012; Ghatak *et al*., 2010; Voora *et al*., 2009).

The study clearly indicates that myalgias are more common in females as compared to males. However the CPK levels were significantly higher in males as compared to females which depicts that males were more susceptible to myopathy. Furthermore myalgias were also dependent on the duration of therapy; these findings are in line with already reported data (Mortensen *et al*., 1997).

Myalgic effect induced by atorvastatin and rosuvastatin has been compared in males and females it has been observed that atorvastatin induces significantly higher myalgic effects in females while rosuvastatin induces the same significant effects in males. No data on this fact is available in literature therefore to confirm these findings further research is required.

In the present study atorvastatin and rosuvastatin induced myalgia was observed, however these differences were unable to touch the level of significance.

CPK has been reported to be a biochemical parameter for the determination of myopathy and the 10 fold increase in

the levels is an indicator of myopathy (Scot *et al*., 2004; Hume, 2015; Mabuchi *et al*., 2007; Ballantyne *et al*., 2003).Therefore raised CPK levels were considered to predict myopathy induced by statins (Sathasivam & Lecky, 2008; Afilalo *et al*., 2007; Methew *et al*., 2007; Thura & Terry, 2011; Samar *et al*., 2016; Brewer, 2003).

In present study 51% of patients were having the complaints of myopathy but only few patients showed elevated levels of CPK. Paul and coworkers has reported that myopathic symptoms can appear in patients who had normal CPK levels.Which concludes that myopathy can also occur with normal levels of CPK or those myalgias may be due to some other reasons (Phillips *et al*., 2002).

Furthermore it was observed that rise in CPK levels were not duration dependent because a number of patients complained the symptoms of myalgia rather their CPK levels were not elevated. It has also been observed that extent of myalgia was duration dependent as significant relation was observed between myalgia and duration of statin use. No supportive data is available to confirm these results and further research is required to indorse these outcomes.

CONCLUSIONS

The results depicted that males were more prone to ischemic heart disease as compared to females. It was further concluded that females were more prone to myalgic symptoms as compared to males however the elevation of CPK levels were prominent in males which shows that male were more prone to myopathy The data depicted that myalgic symptoms and rise in CPK levels were dose related which means as the dose increases the extent of muscle problems also increases. It was further concluded that myalgia directly related to duration of statin use.

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