Original Article

Myopathies Associated with Statins Use in MI Patients

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ABSTRACT

Objective: To determine the spectrum of myopathies in patients of MI after taking statins.
Study Design: Observational / case-control study.
Place and Duration of Study: This study was conducted at the Ayub Medical Complex, Abbottabad. It was conducted from Dec 2013 to May 2014.
Materials and Methods: The study involved 100 known MI patients on statins of different ages and 100 control subjects. Their history regarding duration, dose, and muscle pain was taken and blood was collected for serum CPK. A relationship between duration of statin used and musle symptoms were studied.
Results: chi-square test gives 10.4904 which is significant . The p-value is .0012. This result is significant at p < .05. There is a positive assosciation of CPK levels and muscle pain with odd ratio of 20.9. which shows a positive association .and 95% confidence interval shows a significant association with 9.7-41.4.p<0.000 which is highly significant.
Conclusion: The study concluded that long term unchecked therapy of statin can cause severe damage to the body muscle even the heart muscles. So there should be proper follow up after 2-3 months to protect the patients from fatal myopathic effects.
Key Words: Myocardial infarction, Statins, Myopathies and Serum CPK levels.

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INTRODUCTION

Myocardial infarction (MI), also known as a heart attack occurs when blood flow decreases or stops to a part of the heart causing damage to the heart muscle[1]. It is explained as a threat that leads to severe tensions in one's whole life and it is also a serious family stress especially for the couples[2]. According to WHO (2011) 14 million people die every year[3]. Risk of Myocardial Infarction Study (PROMIS) was conducted, in Pakistan a country with a population of 175 million only 1,000 patients and same number of controls had been assessed in all available epidemiological studies of CHD[4]. WHO's (World Health Organization) criteria of myocardial infarction is as follows; Characteristic chest pain (usually more than 30 minutes) and diagnostic electrocardiogram (ECG) changes. Rise and subsequent fall of serial levels of cardiac markers. Chest pain may travel into shoulder, arm, back, and neck or jaw often on left side[5].

In western countries, MI is commonly seen in elderly men of the age of forty and atherosclerosis is the major underlying cause[6]. Atherosclerosis is a state in which plaque builds up within the arteries and it is made of cholesterol, fatty substances, cellular waste products, calcium and fibrin (a clotting material in the blood)[7]. In long term management with all others, statins are very important. Recent statistics demonstrate increasing statin use in patients with elevated atherosclerotic cardiovascular risk[8]. Statins are the most effective medicines in the prevention of atherosclerosis and thereafter myocardial infarction, these reduces the risk of both morbidity and mortality by effectively lowering LDL level and these are the best selling medicine in controlling cholesterol in blood[9]. Although statins are very good, but the associated myopathies are the most prevalent and important adverse event. About 72% all adverse events are being muscle related., and the most common one is skeletal muscle toxicity[10].There are several factors that predispose patients to muscle-related adverse effects. These include advanced age (>80 years), female sex, Asian ethnicity, low body mass index[11]. All statins have the capacity to develop muscle toxicity but severity varies widely among statins[12]. Statin induced myopathy is a vast term including disorders ranging from myalgia to lethal rhabdomyolysis now known as (SAMS)[13]. Rhabdomyolysis is a well-documented side effect of statin therapy[14]..It is characterized by muscle necrosis

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and the release of intracellular muscle constituents into the circulation. Creatine kinase (CK) levels are typically markedly elevated, and muscle pain and myoglobinuria may be present[15]. To evaluate the statin adverse effects CPK levels are measured. Patient management through evaluation of CPK levels physician often measure serum CPK levels as a clue for severity of statin-induced muscle toxicity. Creatine phosphokinase (CPK) is an enzyme also known as creatinine kinase or phospho-creatin kinase. This enzyme basically catalyses the alteration of creatinine and use of Adenosinetriphosphate (ATP) to phosphocreatine and ADP.[16] The frequency of statin myopathy is reported more frequently in clinical practices, since RCTs are not explicitly designed to assess myopathy and the patient population studied does not reflect the same population. Indeed, observational evidence estimates that skeletal muscle myopathies occur in 10-15% of patients[17,18,19]. All statins have been implicated in causing muscle side effects, but at differencing frequencies. The in vitro level order for statin cytotoxicity has been reported to be more in cerivastatin than in simvastatin acid, fluvastatin, atorvastatin, lovastatin acid, pitavastatin, rosuvastatin, pravastatin[20]. Myopathy related with statin usage can begin as early as one week into therapy but onset also can be late for several years. On average, myopathy is reported to occur 6 months after starting therapy[21]. Muscle complaints from statins are dose dependent, of diffuse origin[22] and often result in the structural damage to muscle fibres which can persist even after discontinuation of therapy[23]. To combat severe adverse events patient more hospitalizations which could lead further expenses on drugs. Increasing the burden of healthcare expenditures and the drug interaction could increase the risk of muscle disorders or increased CPK levels ten folds[24]. Asian are more sensitive in its clinical response to statins than is the Western population, and for this reason dose of statin for Japanese are relatively low compared with those prescribed in the USA[16]. In hospital serum CPK levels can predict the severity of statin-induced myotoxicity but the link between symptoms and CPK level is not very clear. Though the explanation of CPK level is complex and hence there is not a compromise on the explanation of statin myopathy by The American College of Cardiology[25], FDA.) At present, the different studies supports three diagnostic ways: Initial myopathy (CPK above 3-fold the ULN, less than 10-fold the ULN), Myopathy (CPK above 10-fold the ULN, less than 50-fold the ULN), and Rhabdomyolysis (CPK above 50-fold the ULN)[26]CPK levels are not routinely measured.

MATERIALS AND METHODS

The purpose of present study was to assess the spectrum of statin induced myopathies in Pakistani population. The study was conducted in the Department of Biochemistry Hazara University Mansehra and Ayub Teaching Hospital. Samples were collected from patients visiting outpatient department of ATH Abbottabad. It was an observational study (case/ control). The study include 200 subject divided in to two groups. Study group consists of 100 patient of MI on statins between the age of 25 and 80 yrs. Control Group consist of 100 age and gender matched non MI patients. Convinent sample technique was used on 100 known MI patients satisfying the criteria of WHO for myocardial infarction and controls were 100 age and gender matched having no heart disease like MI. Cases included were Patients of myocardial infarction on statins between 25 to 80 yrs of age of either gender. Age and gender matched subjects having no heart disease (MI**)** were selected as Controls. Exclusion criteria for Cases Recent i/m injection: Patient should not receive Intra muscular injection before the performance of CPK because any prick or injury of musle cans raise CPK, exercise can raise the CPK level, Muscular trauma: Any injury to the muscle can raise the CPK level and Prolong immobilization can raise the CPK level. Controls excluded were Patients of Myocardial infarction, patient of any muscular disease, Recent i/m injection: Patient should not receive Intra muscular injection before the performance of CPK because any prick or injury of musle cans raise CPK, Any heavy exercise can raise the CPK level, any injury to the muscle can raise the CPK level and prolong immobilization can raise the CPK. After taking informed consent, the purpose of the study and its procedure was explained to the patients. Data was collected on predesigned Performa containing name, age, sex, occupation, medical and, drug history and history of muscle pain. Blood was collected from controls and cases both male and female by using standard aseptic technique. And then perform the CPK test on the sample. Data was entered into computer, analysed by using SPSS version 21 and mean ± SD significance odd ratios and confidence interval (CI) were calculated. After taking informed consent, the purpose of the study and its procedure was explained to the patients. Data was collected on predesigned Performa containing name, age, sex, occupation, medical and, drug history and history of muscle pain**.** Blood was collected from controls and cases both male and female by using standard aseptic technique. And then perform the CPK test on the sample.Data was entered into computer analyzed by using SPSS version and mean ± SD significance odd ratios and confidence interval (CI) were calculated.

RESULTS

A total of 200 participants, 100 cases and 100 controls were studied for myopathies and CPK levels. Chi Square for the group having muscle pain with raised

CPK levels was 34.2 and p value was found highly significant (P<.0.005) as shown in table 1. The odd ratios were taken shown in table 2. These showed a positive association of CPK levels with muscle pain and 95% confidence interval showed a significant association, which strengthen the results, p-value showed a very highly significant result.

History of muscle pain was of different grades (mild to severe) are shown in Figure 1. The frequency distribution of muscle pain was 25% with no pain, 44% mild pain, 17% moderate and 14% patient on statins showed severe muscular pain. We also studied the different levels of CPK in muscle pain like normal and raised CPK level in patient of myocardial infarction who are taking statins (lipid lowering drugs). In first group these were 69% with raised CPK and 6% with normal CPK having muscle symptoms. In second group 9% with raised CPK and 16% with normal having no muscle pain shown in Figure 2.

Table No.1: Chi Square for the group having muscle pain with raised CPK.

	Test statistic(chi sq)	p-value	Result
CPK and muscle pain	34.2	0.000	Very highly significant

Table 1: Shows the Chi Square for the group having muscle pain with raised CPK levels that was 34.2 and p value was 0.000 which was found highly significant P<.0.05 .

Table No.2: Positive association of CPK levels and muscle pain.

Statistics	Values	Results
Odd ratio	20.9	Positive association
95% Confidence interval	9.7-41.4	significant
p-value	0.000	Very highly significant

Table 2: Shows a positive association of CPK levels and muscle pain. The odd ratio of 20.9. which shows a positive association. and 95% confidence interval shows a significant association with value 9.7-41.4.p<0.000 which is very highly significant.

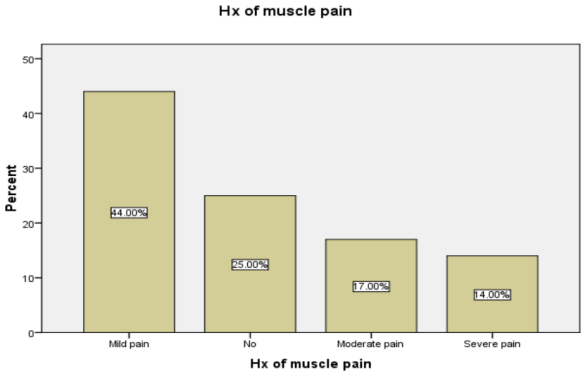

Figure No.1: Frequency distribution of muscle pain

Figure.1Shows the frequency distribution of muscle pain was 25% with no pain, 44.00% mild pain, 17.00% moderate and 14.00% severe.

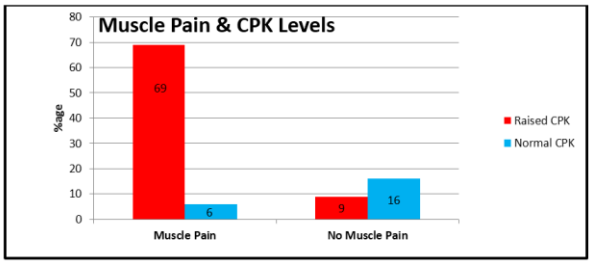

Figure No.2: Muscle pain and CPK level

Figure 2 shows the comparison of muscle pain with normal and raised CPK level in patient of myocardial infarction who are taking statins (lipid lowering drugs). In first group there were 69% with raised CPK and 6% with normal CPK having muscle symptoms. In second group 9% with raised CPK and 16% with normal having no muscle pain.

DISCUSSION

Myocardial infarction is a very important topic of discussion all over the world as it is causing physical, psychological and financial harm to the humans. Even though awerness is increasing day by day but there are some factors which need a proper and strict follow up.but unluckyli some things are not properly monitored by the health care provider and patients both that are causing serious issues.The incidence of muscle symptoms associated with statins was estimated in the observational PRIMO study in patients receiving high dose statins.Myopathy related with statin usage can begin as early as one week into therapy but onset also can be late for several years. On average, myopathy is reported to occur 6 months after starting therapy[27]. In a study by ISIS on non-Pakistani population (14,000 cases of acute myocardial infarction (MI), 16,000 controls: 95% white British[28],the value of large case-control studies of CHD in relation to genetic and lifestyle factors has been raised.

The present study has pointed out similar issues of muscle damaging by long term use of drugs called "statins". No doubt these are very very effective in preventing" atherosclerosis"a main culprit of MI but there long term use can muscle damage ranging from myopathies,to severe "rhabdomylosis". In this study association of these drugs with myopathies was studied on the basis of elevated serum CPK levels. We find a significant rise in its level and associated muscle pain like complains there were 69% with raised CPK had muscle pain like symptoms.The result of our study was consistent with an earliear study by[29,30]. One can suspect statin-associated myopathy when a statin-treated patient reports an unexplained, generalized muscle pain, tenderness, or weakness. Importantly,

tabout 5.6% in women older than 65 years presents with these symptoms[31]. Another study strengthen my study by saying that statin carry distinct risk factors of muscle pain stiffness, weakness etc[32]. An other study by Karen was similar with this study which proves that, patients with statin-associated myopathies becomes c pain free when they stop taking statin therapy .Hence it proves the myopathic effects of statins[33]. In my study 95% confidence interval shows a significant association with value 9.7-41.4.p<0.000 which is very highly significant when we compare the statins induced high CPK levels similar to the study by Gaist [34] which explained that the comparative risk of muscle damage is of very significance.in addition, Thompson et al indicated that less serious side effect like muscle pain and weakness exist among patients using statins rather than rhabdomyolysis[35].

CONCLUSION

The study concluded that long term unchecked therapy of statin can cause severe damage to the body muscle even the heart muscles. So there should be proper follow up after 2-3 months to protect the patients from fatal myopathic effects.

Author's Contribution:

Concept & Design of Study:	Madeeha Jadoon
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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