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STATIN INDUCED MYOTOXICITY AND ITS CONSEQUENCES - AN OVERVIEW

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ABSTRACT: Statins, 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors, are considered safe in lowering hyperlipidemia and cardiovascular disease. Statin attempt to reduce cholesterol production in liver in dose dependent manner not only cause the muscle related problem but also leads to other untoward consequence like arthritis, diabetes, neurological disorders which arise as a result of scarcity in cholesterol production. Discontinuation or reduction in the dose of the statin usually leads to resolution of these side effects but the efficacy is questionable. Though the statin had come to market several decades ago, their harmful effects have been well understood very recently only after several randomized trials. The pleiotropic effects of statin have reported many benefits, but lack of randomized clinical trials make it limit to extend its indication beyond lipid lowering effects. There is still a controversy between their benefits and adverse effects of statin. The upcoming research should focus to resolve the above said confliction that could overcome its most adverse events- myopathy. If it so the statin with pleiotropic effect without any myopathic symptoms would be an excellent candidate among all other drugs. In this review, we discussed the myotoxicity, mechanism of myopathy, consequences as a result of statin's attempt to reduce cholesterol production, risk factors for myopathy.

INTRODUCTION: Stain, the 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CO A) inhibitors, are the most prescribed and first choice class of drugs in the treatment and management of hyperlipidemia and related cardiovascular diseases (CVD).[1] These have been long-established in reducing cardiovascular morbidity and mortality in low to high risk patients.[2] From the introduction of Lovastatin in 1987 to pitavastatin of late the research has not been ruined in findings of beneficial to adverse events of statin. [3, 4]

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The population reported for statin induced myopathy is significantly less in clinical trials due to restricted criteria followed but it is more in case of observational studies.[5, 6] In large clinical trials [7] the efficacy and safety of statins have been well acknowledged but after long-lasting use of these drugs in unselected population of outpatients (findings from observational studies), [8] it has been reported to have unrecognized troublesome adverse effects. [9]

Various adverse events had been reported and range from mild to severe. Among these, muscle (ranges from myalgia to rhabdomyolysis) and liver toxicity are major one in which hazard increases due to higher dose, interacting drug and genetic predisposition leading to death.[10, 11] These are not covered during preclinical testing of statin, but reported during clinical studies and some other

statemented only after post marketing surveillance even they succeed FDA approval. One such great example was cerivastatin withdrawal from market [12] and another one was issues about rosuvastatin (wolfe petition recommended to remove it from market) regarding its muscle and renal toxicity. [13] FDA announced new safety recommendation for high dose of simvastatin which shows increased risk of myopathy after using 80 mg. [14]

However the use of statin has extended considerably and statin related muscle complications are becoming wholly characterized. But the precise determination of statin induced myotoxicity in large measure become hard because of widespread diversity in its clinical representation. This review gives recent findings in statin muscle toxicity including risk factors, mechanism of muscle toxicity and its consequences.

2. Myotoxicity – general:

Myopathy is common term to describe mild (Myalgia) to severe muscle toxicity (Rhabdomyolysis) produced by statin use. Rhabdomyolyis is characterized by release of cellular content into bloodstream especially myoglobin leading to kidney damage and death. Modest compromise exits on how to define myotoxicity of statin[11] which may give the under diagnosis of this complication. Organizations like American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI), National Lipid Association (NLA) and US Food & Drug administration (USFDA) have standardized the terminology for myopathy yet they all differ in their definition.

According to ACC/AHA/NHLBI clinical advisory board myalgia is muscle pain or weakness with normal creatinine kinase (CK) levels, myositis is myalgia with increased CK levels and rhabdomyolysis is muscle symptoms with marked CK elevation (>10×ULN). But as per USFDA rhabdomyolysis is muscle symptoms with marked CK elevation >50×ULN or 10,000 IU/L with renal compromise.[15] The greater part of randomized controlled trials with statins defined myopathy as an increase in CK (creatinine kinase) > 10 times the upper limit normal (ULN) with [8] or without muscle symptoms.[16] As a consequence of this difference in definition of myopathy, the reported incidence of myopathy in different clinical trial differs in their results.[8, 16]

In randomized controlled trials of statins there was very low risk of myopathy similar to that of placebo. In trials 12,064 subjects were randomized to 20 to 80 mg simvastatin there were 49 cases of definite myopathy in simvastatin 80 mg group and 2 in 20 mg group.[17, 18] On the contrary to the low incidence of myopathy in randomized trials, higher incidence of myopathy has been reported in observational studies.[11, 17] This may be due to failure to report or document the mild symptoms, application of strict criteria to define myopathy, trials are designed to assess only efficacy but not mild muscle pain[19] or primarily due to exclusion of patients with risk factors such as older age, female sex, diseases state (renal/ hepatic insufficiency, history of muscle aches, diabetes) etc in large clinical trials.[9]

All statins can cause muscle toxicity with high doses and also due to drug interactions. But the extent of risk within the therapeutic dose range may fluctuate among statins. This within class variability is due to the statin dosage, the physicochemical properties and pharmacokinetics profile of statin, the concurrent use of agents having drug interaction, genetic factors and other related risk factors (**Table 1).**[10, 20]

2.1 Proposed mechanism of statin induced myopathy

Isoprenylated proteins *Viz* Geranyl phosphate (GPP) and Farnesyl phosphate (FPP) are accountable for the generation of a variety of proteins fundamental in an array of cellular signaling, transportation and transformation processes that boost cell membrane integrity and support intracellular signaling. They also significant in prenylation of various cellular complexes like lamins. Lamins important for structural and functional integrity of nuclei in cells which form a nuclear lamina on the inner wall of the nucleus. GPP and FPP are also originator for essential compound like dolichols and co enzyme Q 10 (ubiquinone) which in turn affects the

formation of protein and energy exchange respectively (**Fig.1**). It has been confirmed after through study that statin induced myopathy is mainly not due to decline in cholesterol synthesis but due to inhibition of the synthetic pathway of cholesterol production consisting of 25 steps resulting in a cutback synthesis of above said vital ingredients.[21, 22]

However, myopathy risk is not related to cholesterol levels alone, there is evidence that increased low density lipoprotein (LDL) receptor sensitivity caused by statins could cause increased intake of fat or plant sterols into the muscle.[23] Recently a theory has projected that vitamin E deficiency as a risk factor for statin induced myopathy.[24]

2.2 Consequences of statin induced myotoxicity:

Cholesterol, essential substance of animal cell, act as precursor for Vitamin D3 and sex hormones and helps in preventing cell membranes oxidation and in immune mechanism. But excess cholesterol is deposited in the artery walls as it travels through the bloodstream and gobble up with special cells in the artery wall, creating a lump in the artery wall which then develops into plaque. By lowering the cholesterol content using statin in unstable plaques will make them more stable and less prone to rupture by reducing heart attack.

But this life saving use of statin (which designed to reduce cholesterol synthesis) unfortunately leads to major consequences. It is believed that the inflammation in artery walls are caused due to low fat diet, since statin attempt to lower further cholesterol level, which contribute itself for heart disease and other health problem. The untoward toxic effects produced as a result of statin attempt to decrease cholesterol synthesis is schematically represented in **Fig. 2**.[25–38]

3. Factors aggravating myotoxicity:

There are various predisposing factors possibly enhancing the risk of statin induced myopathy are summarized in **Table 1**.[11, 23, 39]

TABLE 1: FACTORS AGGRAVATING MYOPATHY RISK

Patient factors			
Age Sex Body frame/fragility	Complex medical problem Hypothyroidism. Impaired renal & liver function. Diabetes. History of myopathy. Inflammatory metabolic muscle defects. Biliary tract obstruction. Bacterial/viral infections.	Habit Alcoholism. Drug abuse. Intense physical exercise.	Others Surgery. Trauma. Polypharmacy. Polymorphism of CYP isoenzyme.
Drug property			
High dose E.g. – Myopathy with 80 mg dose.	Pharmacokinetic variation (within class effect) Statin with High bioavailability. Increased systemic exposure. Lipophilicity. Limited protein binding. Circulating metabolites potency	Drug interaction- co administration with Azithromycin, clarithromycin, erythromycin, cyclosporine (Macrolide antibiotics). Fluconazole, itraconazole, ketocanazole (Anti fungals). Amprenavir, indinavir, ritonair, saquivavir (Anti viral). Nefazodone, amiodarone, diltiazem, verapamil, warfarin, colchine. Grapefruit juice- greater than 1 lit. Glucuronidation inhibitors- gemfibrozil. Nicotinic acid.	

3.1 Age:

Aging causes alterations in body composition and function embracing reduction in hepatic and renal clearance that alter the pharmacokinetic and pharmacodynamics of drugs. In common the majority data prove that statins lower cholesterol in children just as they perform in adults. Generally myostitis, myopathy or rhabdomyolysis haven't been reported in children on statin in randomized clinical trials, only myalgia was reported. The systematic review (7studies) and meta analysis (4 studies) showed significant LDL lowering but showed insignificant side effects.[40]

In adults myopathy occur at a rate of 11 per 100,000 person after chronic treatment, [41] minor muscle aches and myalgias occur at a equal rate in both statin and placebo control groups reported in randomized clinical trials (RCT).[41, 42] But an observational study found that 9% of statin users had myopathic events while only 4% of non-statin users had such events. [43]

Older adults have a reduction of cardiovascular disease, stroke and all cause mortality with statin therapy when compared with younger adults. Even though elderly profit from insistent statin therapy to greater extent than adult,[44] they are less likely to receive a statin prescription.[44, 45] The reason may be concern about adverse event, under representation during early trials, patients with side effects excluded from RCTS, limited life expectancy of older leads to an idea that risk is not worth than benefit. The mechanism of myopathy in elderly is unclear and may be due to age associated factors like decrease in muscle mass [46] and water holding capacity, increase in body fat, commorbitities or taking multiple medications [47] and decrease in serum protein level which result in higher concentration of statin leading to higher toxicity.[48]

3.2 Sex:

Feminine have more risk for adverse drug reaction (ADR) compared to males. The basis is difference in body fat content between men and women. Female tend to have high % of body fat, which influence volume of distribution of some drugs, their half life, including more lipophilic statin. [49] Since women have higher concentration of CYP 3A4, [50] enzyme which metabolize statin, the toxicity is higher which is evidenced by QResearch cohort study, [51] which shows two-fold and three-fold increase for myopathic risk in men and women respectively. Women with type 1 diabetes had a five-fold increased risk of myopathy and this clearly indicate that the female patients are affected by myopathy more than male patients if they have risk factors like hypothyroidism, type 1 diabetes, chronic liver disease and hypertension.

3.3 Comorbidities:

Comorbidities on their own participate a major role in changing the statin metabolism and clearance from the body. Physical condition that could possibly direct to an accumulation of statins in plasma is considered to be a risk factor for statin-induced myopathy. [52] Hepatic and renal insufficiencies, diabetes and metabolic syndrome are examples of conditions that has been reported to amplify the levels of statins in plasma.[53] But many cardiologists prescribe statins to all patients (people with Type II diabetes also) over a certain age regardless of whether they have metabolic syndrome. This let Food and Drug Administration to warn (new labeling) about the drugs, especially when taken at higher dosage levels.

- Management of Hyperlipidemia or cardio vascular drugs (CVD) with high potency statins chiefly with atorvastatin, rosuvastatin and simvastatin may increase the risk of developing diabetes. Study with 153,840 women without diabetes and with a average age of 63.2 years, after adjusting for other potential variables, including age, race/ethnicity and body mass index found 10,242 new cases of diabetes when adhered to statin use (all statin). This study concluded that diabetes induced by statin is a medication class effect and not related to potency or to individual statin.[54]

- The several factors is said for increased risk of new-onset diabetes among patients receiving certain statins including impaired insulin secretion and inhibited insulin release.[55] Coenzyme Q10 depletion caused by statin induce not only muscle fatigue and also the reduced expression of GLUT4 (protein, which is part of the cellular response mechanism, along with insulin, that helps to control blood sugar levels) which in turn contributes to insulin resistance and the onset of type-2 diabetes. The effect were found more with lipophilic statin compared to hydrophilic drug. [56] Thus the patients with history of diabetes will have more risk for myopathy then the patient with new onset of diabetes when treated with statin.

- Studies have found the relationship between statin myopathy and hypothrodism. The defects in glycogenolysis or impaired mitochondrial oxidation are responsible for this effect. Theories for the cause of statin induced

myopathy was proposed that this is due to reduction in small guanosine 5'-triphosphate–binding proteins and reduced cholesterol synthesis causing skeletal myocyte membrane instability. These mechanisms are synergistic when higher dose of statins are prescribed to hypothyroid patients.[57, 58]

3.4 Other factors:

- One of the most striking metabolic abnormalities produced by chronic alcohol abuse is the gradual reduction in muscle mass, which appears to be associated with the atrophy of fast twitch (Type II) fibers leading to myopathy. Statin, causing oxidative stress in mitochondria, disturbance in protein synthesis, vitamin D deficiency together synergizes the myopathy effect when used by alcoholist.[53, 59]

- Augmented physical activity has been concerned with statin-induced myopathy [60] which is evidenced by study at the Bostan Marathon with increased skeletal muscle injury; CK elevations in statin users compared to non statin users.[61] It is evidenced that statins possibly will up regulate muscle cell apoptosis (oxidative stress), inflammation and protein catabolism in response to unusual exercise and that statin therapy may negatively influence the firmness of skeletal muscle cell membranes with elevated CK. This is reason for more distinct muscle damage up regulating inflammation which consecutively report for the longer recovery time for exercising patients.[62]

3.5 Polymorphism:

Since statin induced myopathy is a plasma concentration dependent adverse reaction, polymorphism in CYP isoenzyme and drug transporters concerned in disposition of statin might induce pathopharmacology of statin especially simvastatin which in turn associated with myopathy.[63, 64] Though statin-induced CK elevations are dose-dependent, the relationship between plasma levels of statins and the risk for statin-induced myopathy has not been constantly demonstrated across populations.[65] Some investigators have suggested that a synergistic interaction between genetic and pharmacological factor might be reason of statin myopathy. [66] It has been proposed that statin-induced myopathy is correlated with a single-nucleotide polymorphism with intron 11 of the SLCO1B1 gene on chromosome 12. [67] Statins penetrate hepatocytes through organic anion transport polypeptide (OATP) 1B1, which is coded by the SLCO1B1 gene.[68] It was statemented that plasma statin concentration liable to be higher in people with the above polymorphism, in consequence predisposing them to adverse effects.[67, 69] On the other hand, modern studies have shown that this polymorphism might be largely associated with simvastatin-induced myopathy.[70]

It was identified by SEARCH collaborative group that rs4149056 polymorphism of SLCO1B1 (521C variant) was associated with a 4.5 fold increased risk of myopathy in heterozygotes and 17 fold higher risk in homozygotes when co administered with simvastatin 80 mg daily. [71] Study of Voora et al[72] found the larger risk of side effects with the high doses and also pointed out the patients with this polymorphism have 2 fold relative risk. A retrospective case-control study involving 137 subjects taking simvastatin as a concomitant medication reported that non exercise-induced CK elevation was associated with homozygosity in a genetic variant of the CYP3A enzyme, CYP3A5*3, which led to a greater degree of muscle damage. [73] The one observational study demonstrated that the SLCO1B1 388A>G and 521T>C polymorphism were associated with a lower risk and higher risk of statin respectively stating role of SLCO1B1 polymorphism in statin tolerability[74] and risk is higher in native American having this polymorphism.[75]

One more study identified three genes – COQ2, ATP2B1, and DMPK – that are accountable for pathways related to CoQ10 biosynthesis, calcium regulation in the body, and muscular dystonia, respectively, as markers for myalgia in patients having statin-associated myalgia.[76]

3.6 High dose/ individual drug effect:

Statin induced myopathy is considered to be dose dependent. As per the cases reported by USFDA, the highest rate of fatal rhabdomyolysis was noted

with cerivastatin. This is was due to prospective drug interaction and high dose which led to withdrawal of cerivastatin while there were no fatal cases with fluvastatin. The rate of occurrence of fatal rhabdomyolysis was found with pravastatin and atorvastatin are 0.04, with simvastain 0.12 and with lovastatin is 0.19.[77]

The hazard of statin induced muscle toxicity is more liable with higher doses and appears to be more evident with simvastatin dose 80 mg confirmed by SEARCH TRIAL[78] (lead to warning by FDA in use of high dose of simvastatin). In PRIMO STUDY[6] 18.2% of patients on high dose of simvastatin 40-80 mg experienced muscle toxicity compared with 5.1%- fluvastatin XL 80 mg, While atorvastatin and pravastatin have intermediate effect.

The safety of higher doses of atorvastatin has been assessed in more than 11,000 patients and insignificant rate of myopathy was observed[79] and reason might be the lack of dose dependency of muscle adverse effects with atorvastatin.[80] In contrast to above one observational study in unselected population of 7924 patients with hyperlipidemia (France) reported that 14.9% of patients receiving atorvastatin 40-80 mg experienced muscle symptoms[6] and the prevalence of muscle related adverse events was considered to increase 4 to 5 fold when dose of atorvastatin was increased from 40 to 80 mg.[80]

A meta analysis of 19 randomized statin trials comparing standard doses of all statins except rosuvastatin accounted that fluvastatin was associated with the lowest rate of myopathy compared to other statin.[81] The rosuvastatin dose upto 40 mg have no muscle toxicity but the higher doses appeared to be associated with increased risk of myopathy.[82] The incidence of myopathy might be increased with higher dose of pravastatin and pitavastatin but there is lack of well assessed randomized trials.[83, 84]

There is no conclusive evidence whether there is any difference between various statin in risk of inducing myopathy due to lack of randomized trials. With available data it is understood that an estimate of potential for causing myopathy among the currently available statins, from least possible to most possible is pravastatin, fluvastatin, rosuvastatin, atorvastatin, lovastatin and simvastatin. This variation in incidence of myopathy influenced by dose among same class of drug is attributed to difference in Pharmacokinetic properties of individual drug which discussed in following head.

3.7 Physicochemical, Pharmacokinetic properties/ potency - causes of myopathy:

Statin pharmacological properties that are associated with statin induced myopathy include high bioavailability and systemic exposure, lipophilicity, limited protein binding, presence of circulating metabolites and drug interactions via CYP450 isoenzyme or glucoronidation pathways.[23, 85]

Lovastatin, simvastatin and atorvastatin are metabolized by CYP3A4, rosuvastatin minimally by CYP2C9, fluvastatin by CYP2C9 while pravastatin undergo sulfation. Among statin metabolized by CYP3A4 isoenzyme, Lovastatin and simvastatin are considered as sensitive substrates because their levels increased 5 fold or higher by CPP3A4 inhibitors while atorvastatin interact lesser extent.[86] Simvastatin is likely to be more sensitive to CYP3A4/5 inhibition than atorvastatin because extensive first pass metabolism results in systemic bioavailability less than 5% (atorvastatin 12%).[87] Pitavastatin minimally metabolized by CPY450 enzyme are expected to have a lower risk of drug- drug interaction and related adverse effects.[88]

Pravastatin, fluvastatin and rosuvastatin are hydrophilic and thought to penetrate less likely to myocyte membrane compared to more lipophilic statin viz simvastatin, lovastatin and atorvastatin for which higher incidence of myopathy was reported due to higher penetration.[46, 89] Being hydrophilic rosuvastatin generally require higher dosing for efficacy but it not so and associated with lower incidence drug interaction and thereby less adverse events. Rosuvastatin is considered to be most potent with longest half life, [90] so high dose may lead to more adverse effects. [91] Fluvastatin and atorvastatin are minimally excreted in urine and safety in kidney disease patients. Bile tract

obstruction patients will have increased risk of myopathy as bile is primary route of excretion of statins. Since gemfibrosil affect glucoronidation pathway of statin it lead to toxic level of statin.[92]

From pharmacokinetic standpoint, rosuvastatin and fluvastatin have a profile to yield fewer or no adverse events since it have high hepatoselectivity, low distribution in muscle cell due to hydrophilicity, highly bound to serum protein, low rates of metabolism via CYP450, little tendency of drug interaction and low or moderate systemic bioavailability.[93] But all this benefits may be overhidden by other factors such as potency. The potency emerges to be fundamental predictor of adverse effect reporting risk. Fluvastatin having lowest potency was not often prescribed but associated with 74% of adverse effects. So being high potency the rosuvastatin and fluvastatin may lead to higher incidence of myopathy while atorvastatin and simvastatin showed intermediate risk, pravastatin and lovastatin appeared to have lowest risk.[91, 94] Therefore merging both pharmacological properties and potency it's tough to predict the statin with expected safety profile. More head to head randomized control trials are desirable to resolve this issue.

3.8 Drug interactions:

More than half of statin related rhabdomyolysis cases engrosses two important features, one is interaction with agents that share statin metabolizing pathway and another is hindrance of transporter system (by the specific drugs) that is responsible for hepatic uptake and excretion of statin.

Co administration of a statin with drugs *Viz* Cyclosporine, macrolide antibiotics, anti virals etc (**Table 1**) metabolized by the same CYP3A4 isoenzyme elevate the statin level and risk of myopathy. The risk is fewer with fenofibrate than gemfibrosil, this may be because gemfibrosil restrains hepatic glucuronidation of statins, there by interfering with statin elimination.[92] Regardless of the hypothetical benefit of co administration of statin which is not metabolized by CYP3A4 isoenzyme with CYP3A4 inhibitors there still stays a modest risk of myopathy due to other metabolic and transporter mechanism.[95]

The organic anion-transporting polypeptide (OATP) 1B1 (gene name SLCOB1) arbitrates the hepatic uptake of all statins to a inconsistent level and the efflux transporters P-Glycoprotein / the breast cancer resistance protein (BCRP, gene name ABCG2) are engaged in the transport of most of the statin from the hepatocytes into bile.[96, 97] Therefore drugs like cyclosporine, diltiazem that inhibit P-Glycoprotein may increase statin levels and precipitate toxicity.[98] With narrow therapeutic range drugs such as warfarin and digoxin statin increase anti coagulation effect, the reason expected to be that statin (simvastatin) inhibit metabolism of warfarin through CYP2C9.[87]

DISCUSSION: The statin, indicated for lowering LDL-C is considered to be a life saver from 1980s for low and high risk cardiac patients. The cerivastatin withdrawal (due to myotoxicity) made researcher to aware of adverse effects produced by statin and more randomized control trials and observational studies confirmed the life threatening effects of this life saving drug. This focus on the adverse event mechanism fortunately leads to the beneficial effect of statin through its pleiotropic effect which arises as a result of blockage of production of important key products in de novo synthesis *viz* isoprenoids.

The endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response are some of reported pleiotropic effects. Other beneficial effect reported are effects on the immune system, CNS, bone, in cancer treatment [99] and in acute coronary syndrome [100] etc. These effects have been well explained in many review and research articles from past few years.

In contrast to studies reporting positive effects on survival, clinical status and cardiac function in heart failure, two large RCTs[101, 102] have not yielded significant improvements of the primary endpoints in patients treated with rosuvastatin compared with placebo. The article published in natural news explained the negative impact on the pleiotropic effects of statin.

In general the inflammation is caused due to low fat diet. Since statin attempt to lower further

cholesterol level it contributes itself for heart disease and other health problem. In contrast to above statement, studies have reported the anti inflammatory effect of statin.[103] One side it block the production of important antioxidant coenzymeQ10 causing oxidative stress, myopathy and death. On the other hand it preserves endogenous antioxidant superoxide dimutase improving endothelial function.[104] Decrease in caveoline production by statin tend to produce arrhtymias/ cardiac arrest, in contrary it was reported that less caveoline production by statin cause increased production of NO which in turn dilate the blood vessels.[104] The risk factor for statin myopathy restricted the use of this drug in renal, diabetic and elderly patients (**Table 1**). But now clinical studies have explored the beneficial use of statin in patients with above said risk condition.[105]

The conflicting results of these studies make us to confound whether the pleiotropic effects balance the harmful effects caused by statin which inhibit the cholesterol a vital nutrient for well being. This is the biggest challenge of researcher to clarify the above question through their research findings.

Some alternate approaches have been proposed to reduce the adverse events in treatment of hyperlipidemia. The researchers at Brigham and Women's Hospital have revealed that in patients previously on a statin, the addition of a new drug, called AMG 145, can lessen LDL cholesterol levels by up to 66% after 12 weeks. AMG 145 is a monoclonal antibody, binds to a protein that normally drives LDL cholesterol receptors for destruction. By blocking that protein, AMG 145 guards the receptors from being devastated, thus increasing the number of LDL cholesterol receptors on the surface of the liver that facilitate removable of bad cholesterol from the bloodstream. The highest dose given every two weeks also allowed 93.5% of patients to achieve the most tough cholesterol-lowering goals without serious adverse events.[106]

Another finding demonstrated that microRNA-30c (miR-30c), a genetic regulator, interacts with MTP (Microsomal Triglyceride transfer Protein, contribute to hyperlipidemia) and induces its degradation, leading to reductions in MTP activity, the production of lipoproteins, plasma lipids, and atherosclerosis. This molecule also reduces lipid synthesis independently of MTP thereby avoiding complications associated with drug therapies aimed at lowering lipoprotein production. The authors conclude that a medication mimicking miR-30c could potentially be effective in reducing hyperlipidemia in humans without producing any serious side effects.[107]

Introduction of new drug entities to a market will take the lifespan of a human. The technologies like nanoformulation encompassing the natural agents having own hyperlipidemic action have benefits like negligible side effects, bypassing first pass metabolism with controlled release of drug, targeted action, reduced dose and increased bioavailabilty might give resolution for this issue. So more research has to be focused in formulating new dosage form of existing statin molecule to bypass the statin induced myopathy ranging from myositis to rhabdomyolysis.

CONCLUSION: Statin, the first line drug for the management of cardiovascular disease, have serious muscle related problem. Though the clinical studies show the insignificant result in myopathic effects, the percentage of population related to this problem is more in case of observational studies. The statin by blocking the mevalonate production leads not only cholesterol reduction also reduce the major key products for cell activities like coenzyme Q10, isoprenoids etc. This leads to untoward effects, sometimes the adverse effects may also be cardiovascular crisis for which statin is prescribed. This problem aggravates if patients exhibit some risk factors like diabetes, alcoholism, genetic mutation, exercise etc.

The risk is more in female elderly with multiple diseases. Among seven statin available, it has been reported in randomized trial that simvastatin is most dangerous statin and some other as rosuvastatin. Though many altered treatment strategies like combination therapy and inclusion of coenzyme Q10 and vitamin D supplement etc are followed to reduce adverse effects and to benefit lipid lowering, the end result is not that much appreciable and outcome of long term usage is myotoxicity.

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