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RESEARCH ARTICLE

THE RECENT CHRONIC-INTENSIVE USE AND DYNAMIC FUTURE OF STATINS : RISKS VS BENEFITS

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ABSTRACT

The increased HMGco A reductase therapy in the field of cardiovascular disease can be well explained by potent LDL and total cholesterol lowering ability. About 5 to 7.78 percentage of Indian population receiving daily statin therapy. Since statins are less suspected for its long term events, the improved understanding of long term effects of commonly used statins are necessary to reduce the accumulation of drug induced complications in hospitals. Long term effects of statins include neuropsychiatry adverse effects like cognitive impairment, dementia and short term memory loss. Diabetics, risk of carcinoma, interstial lung disease, and myopathy were few among vast data. In CAD and CKD patients, long-term statin therapy reduced the rates ADR and death rates and also statins can decrease the intra-hepatic vascular resistance in a cirrhotic liver and improves the flow mediated vasodilatation of liver vasculature. In the treatment of neurological diseases like multiple sclerosis, stroke and Parkinsonism statins shows a benefited effect. Statins are used for treating endometriosis, excessive angiogenesis and invasion of endometrial endothelial cells which is associated with locally elevated inflammatory cytokinesis. The improved understanding of long term effects of commonly used statin can considerably reduce accumulating drug induced complications in hospitals.

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INTRODUCTION

Dyslipidemia is elevated total cholesterol, low density lipoprotein (LDL) cholesterol, or triglycerides. The common practice after diagnosing dyslipidemia is initiating statin therapy immediately without considering lipid levels. The increased HMG CoA reductase inhibitor therapy can be well explained by potent LDL and total cholesterol lowering ability. The percentage of the Indian population receiving daily statin dose increased from 3.35 to 7.78, because of the cardiovascular burden in the country. [1] Many large clinical trials suggests that patients undergoing statin therapy for an average of 5 years can reduce the incidence of morbidity and mortality in patients because of CHD (Coronary Heart Disease) and stroke. [2, 3] Since statins are less suspected for its long term events, the improved understanding of long term effects of commonly used statins are necessary to reduce the accumulation of drug induced complications in hospitals. This intensive use of statins as monotherapy or combination therapy in all cardiovascular diseases calls the need of risk Vs benefit study. In most cases, the benefits of chronic use of statins in cardiovascular complication highly outweigh risk. Hence this review focuses on creating awareness on long term –intensive use of HMG CoA reductace inhibitors and its impact on comorbid condition.

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Historical perspective of statins

The cholesterol was first isolated from gallstone in 1784, which was a mile stone in medical history .It was followed by serious cholesterol research on biosynthesis of cholesterol. In 1950's, it was well known that the only possible way to decrease the risk of coronary artery complication was to reduce cholesterol biosynthesis. [4] Insite of above knowledge, research have come across many decades and scientist could develop remarkably effective cholesterol lowering agents which lead to statin saga. The late 1980's introduced first generation statins (lovastatin, pravastatin and fluvastatin)which marked the beginning of statin saga, followed by second generation (atorvastatin and simvastatin) which are the widely prescribed statins, have the ability to reduce greater than 30% LDL comparing to first generation. The third generation includes rosuvastatin and

pitavastatin. They are called super statins because of their high potency and are reserved for patients at high risk of developing statin intolerance. [5,6]

Long term effect of statin

The major long term effect of statin is cognitive impairment. Almost all widely used statins are associated with memory loss [simvastatin, atorvastatin, pravastatin].[7]One of the study showed that 60 patients who had memory loss were associated with statins, among them 36 were treated with simvastatin, 23 atorvastatin, and 1 pravastatin.[8] Atorvastatin and Rosuvastatin has reported cases of increase in onset of diabetes with long term use. [9, 10] Most of the strong statins were associated with changes in laboratory values of the liver enzymes, HbA1C, CK with short term use itself. [11] The statin has been clinically well known for complication ranging from myopathy to rabdomyolysis. Even genetic basis has been reported for many cases. That is statin induced myopathy has been running families because of the genetic polymorphism of SLCO1B1 gene. The long term effects of statin are summarized in Table 1.

Statins use in CKD

Renoprotective nature of statins is well studied clinically and experimentally. The studies revealed that in CAD and CKD (chronic kidney diseases) patients, long-term statin therapy reduced the rates of both MACE (major adverse cardiac events) and all-cause death/cardiac death by 20.5% and 28.6%/27.7% respectively. [12] One of the Meta analysis concluded that High-intensity statin therapy could clearly reduce the risk of stroke in patients with CKD. [13] Even though useful effects of statins found to be smaller in stage 5 CKD patients and those under dialysis, large Meta analysis support beneficiary effect of statin in less severe renal impairment. [14] The strong statins (atorvastatin, rosuvastatin ,pitavastatin) were more effective in CKD patients while comparing with regular statins (pravastatin, simvastatin, fluvastatin) which had no considerable effect. [15] Beneficial effects of statins include reducing the 24hr urinary protein excretion and are also associated with a rise in GFR. Statins exert its renoprotective action by diminishing the proliferation of mesangial and vascular smooth muscle cells, suppressing mesangial matrix expansion, and inhibiting macrophage infiltration and the production of cytokines so that it reduces the renal injury. [16, 17] The renal and cardiovascular injury is related to decrease NO bioavailability and increased ANG II activation of NADPH oxidase, which further result in vascular oxidative stress and upregulation of vascular proinflammatory gene expression. The role of statins in decreasing the oxidative stress has been widely studied. [18] Among all the HMG CoA reductace inhibitor, atorvastatin use is associated with a significantly larger beneficial effect on the rate of kidney function loss. [19]That is clinically significant risk reduction can be observed from atrovastatin therapy. One of the studies has shown that atorvastatin significantly reduced the proteinuria by 15% to 23.8%. Another study revealed clinically relevant proteinuric benefits from the use of simvastatin in moderate to severe kidney disease, especially those with proteinuria. [20,21] Also statins in combination with ACE inhibitor or ARB in patients with CKD and dyslipidemia considerably involved in reducing protein urea. [22] Further more clinical evidence is needed to support the use of statin in CKD so as to create a more effective treatment plan by adding statins in the management of CKD.

Statins in portal hypertension

Experimental data suggests that statins can decrease the intra-hepatic vascular resistance in a cirrhotic liver and improves the flow mediated vasodilation of liver vasculature. Statins act as true liver selective vasodilators due to its liver selective nitric oxide production. [23,24,25] Similar to other statins, simvastatin increases nitric oxide production by acting on sinusoidal endothelial cells through nitric oxide synthase enzymatic activity. [24] Molecular pathways such as Rho A/ Rho – kinase pathway which are dysfunctional in cirrhosis will be specifically activated by the use of statins and thereby decreases AKT mediated eNOS phosphorylation and over expression of caveolin-1. [26] One of the study suggests that atorvastatin can act by resolving endothelial dysfunction and also blunting inflammatory pathways, thereby reduces the fibrinogenesis.[27] Thus statins seems to be having an important role in the treatment of portal hypertension.[28] A double blind randomized controlled trial concluded that simvastatin can reduce Intra vascular resistance in cirrhotic patients. After 1month of treatment, their hepatic venous pressure gradient (HVPG) reduced to target hemodynamic response without affecting their systemic hemodynamics. [29] Secondary prophylaxis of varicel haemorrhage due to portal hypertension became the new indication of simvastatin.

Statins in neurology

Along with lipid lowering effect, additional properties such as endothelial protection via actions on the nitric oxide synthase system as well as antioxidant, anti-inflammatory and anti-platelet effects of statins might have potential therapeutic implications in various neurological disorders such as stroke, Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis and primary brain tumors. Statins reduce the risk of ischemic stroke and it lowered their risk of having a second stroke by one-fifth on average. But it also slightly increased the risk of hemorrhagic stroke in less than 1% of patients. Evidences from human epidemiological studies, human neuro pathological studies, and experiments using animal models of Alzheimer’s diseases pointed that high levels of cholesterol, particularly low-density lipoprotein cholesterol, were associated with developing of Alzheimer’s diseases.[30] Cholesterol increases the activity of the β- or γ-secretase enzymes that generate amyloid peptide (Aβ) from amyloid precursor protein (APP), decrease the flux of APP through the non amyloidogenic α-secretase pathway, or affect various non amyloid factors, such as local inflammation or tau metabolism.[31,32,33]In the years since the connection between cholesterol level and AD was elucidated, many studies were conducted for use of statins as AD-modulating compounds. The reports of clinical studies suggesting decreased effect of statins in Alzheimer’s diseases creates a dilemma on overall effects of stains in Alzheimer’s disease.[34,35]

Table 1. Long term adverse effects of statins

Statins	Common adverse effects	Long term adverse effects
Lovastatin (10-40 mg/day)	Rash, Stomach cramps, Heart burn, Atrial fibrillation, Eczema, Rhabdomyolysis, Autoimmune myopathy, Tenderness, Dark urine, Dizziness, Yellowing of the eyes or skin, Confusion, Insomnia	Cognitive impairment, Myopathy, Increase in transaminases,
Pravastatin (10-80 mg/day)	Muscle aches, Headache, Constipation, Diarrhoea, Blurred vision, Disturbed sleep, Sexual problems, Chest pain, and Weight loss.	Cognitive impairment, Diabetes mellitus, Breast cancer, Interstitial lung disease.
Fluvastatin (20-80 mg/day)	Chills, diarrhoea, Loss of appetite, Sore throat, Hives, Muscle weakness, Insomnia, Jaundice, Rhabdomyolysis with myoglobinuria.	Liver dysfunction.
Atorvastatin (10-40 mg/day)	Abdominal pain, Dyspepsia, Constipation, Jaundice, Fatigue, Insomnia, Thrombocytopenia.	Cognitive impairment, Diabetes mellitus, Hepatic cirrhosis, Pancreatitis, Aplasia, Rabdomyosarcoma, Fibro sarcoma, Aspermia, Depression.
Simvastatin (5-80 mg/day)	Fatigue, Heart burn, Bloating, Insomnia, Constipation, Skin rash, Dizziness, Chills, Dark colored urine, Peripheral neuropathy.	Cognitive impairment, Diabetes mellitus, Interstitial lung disease.
Rosuvastatin (5-40 mg/day)	Headache, Myalgia, Insomnia, Constipation, Nausea, Diarrhoea, Rhabdomyolysis, Acute renal failure and liver damage, Weight gain, Jaundice, Dark urine, Clay colored stools, Hoarseness .	Diabetes mellitus, Interstitial lung disease, Depression, Cognitive impairment
Pitavastatin (1-4 mg/day)	Rash, Constipation, Joint pain, Vomiting, Hyperuricemia.	Not available

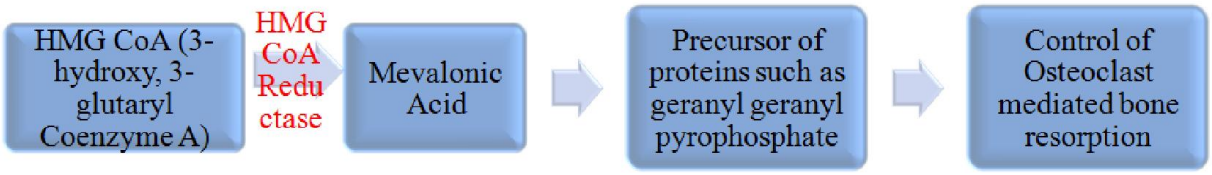

Figure 1. The mechanisam by which statin excert a protective effect on bone

Statins suppress the production of inducible nitric oxide and secretion of tumour necrosing factor alpha by interferon omega which plays important roles in inflammatory process in multiple sclerosis. The immune modulatory effects of statins is defined by binding directly to lymphocyte functional antigen and inhibiting its interaction with intracellular adhesion molecule and this class of drug may be new path to patients with diseases like multiple sclerosis, rheumatoid arthritis and SLE.[36] Protective effect of statins in parkinsonism is described by anti-inflammatory mechanism by glial cell activation, inhibiting oxidative stress, suppressing the aggregation of α-synuclein protein and protecting dopaminergic neurons in animal models of parkinsonisom. Along with above protective mechanism, statins inhibit coenzyme 10 known as ubiquinone antioxidant which plays a protective effect in parkinsonism, thus potentially increasing the risk and worsening the course of parkinsonism. According to these various biologic theories, statins may either have a protective or a deleterious effect regarding parkinsonism.[37] Statins were associated with neuropsychiatry adverse effects like cognitive impairment, dementia and short term memory loss. Simvastatin appeared to be associated with worsened cognition impairment following rosuvastatin, atorvastatin, lovastatin.[38] Pravastatin seems to safer from neuropsychiatric impairment when comparing with other statins. Lower cognitive function associated with statins has found to be more vulnerable to elderly patients, with increased disability. [39,40]

Fracture and statins

The Conversion of HMG CoA to mevalonic acid is inhibited by the statins and this mevalonic acid is the major precursor of cholesterol as well as proteins such as geranyl geranyl pyrophosphate. Antiresorptive action of bisphosponates like alendronate and risendronate is exerted by suppressing the generation of geranyl geranyl pyrophosphate in the mevalonate pathway and it is very important in the control of osteoclast mediated bone resorption [Figure 1]. [41]According to one of the recent study, current statin use excert a protective effect on bone fractures especially fractures of hip, vertebral body and foot.[42,43] However, some of the studies could not observe any effect of statin use on reducing fracture risk.[41,44]

Teratogenic risk of statins in pregnancy

Among those affected, women of reproductive age also with familial hypercholestremia, polycystic ovary disease are in much concern about the teratogenic effects of these medications especially the statins [45]. There is an increase of about 4 fold in the use of this statins in recent decades and reported that 50% of antihyperlipidemic medications dispensed during pregnancy were statins. From a population based study it founds that approximately 1in 100 women used statins or other contraindicated medications during pregnancy [46]. Cholesterol, which is an essential factor for cell reproduction and development naturally increases its level during pregnancy. Therefore the major therapy behind the statin induced teratogenecity is the interruption of cholesterol synthesis [47]. Lipophilicity of statins are considered one of the trigger factor for increasing teratogenic potential since high lipid soluble drugs or chemicals can pass easily across the placenta [48-50].Mostly used lipophilic statins are lovastatin and simvastatin while hydrophilic were rosuvatatin and pravastatin.One of the reason that could lead to poor pregnancy outcome is the interruption of production of dolichol and

isoprenoids which are involved in intracellular signaling and insulin like growth factor system necessary for placental growth by statins[51]. Besides these factors, the women using statins often have comorbid disease states and take concomitant medication that could contribute to congenital malformation. Based on the initial animal studies, FDA categorized the statins as pregnancy category X:contraindicated at any time during pregnancy.

Statins and women health

Statins are used for treating endometriosis, excessive angiogenesis and invasion of endometrial endothelial cells which is associated with locally elevated inflammatory cytokinesis. Currently surgery is the treatment for endometriosis due to anti inflammatory effects but presently statins are investigate for this. Statins decrease endothelial cell invasion, inhibiting excessive cellular growth and decreasing the elevated levels of inflammatory cytokines in endometriosis [52-55]. Another potential use of statins are for the treatment of women with polycystic ovary syndrome. This decrease results in chronic systemic inflammation, elevated serum androgen levels and endothelial dysfunction in a variety of vascular beds [56]. Some studies shows that atorvastatin and simvastatin can decrease circulating androgen concentration compared with placebo and simvastatin therapy resulted in lower androgen levels than the standard therapy with metformin [57,58]. In addition to this, simvastatin and atorvastatin can lower the levels of pro-inflammatory markers in women with polycystic ovary syndrome. [59,60]

Pharmacoeconomic consideration of Statins

All the statins have shown to be effective for reducing the total cholesterol and LDL cholesterol. However considering pharmacoeconomic part, the CER(cost effective ratio: cost/outcome) of statins was very high which increases the need of life style modifications, including dietary changes, exercise and meditation as the preferable choice.[61,62] Atorvastatin is the cheapest statin available comparing to other statins. The statins such as simvastatin, lovastatin or pravastatin were quite expensive. The pharmacoeconomics evaluation studies showed that atorvastatin as the most effective drug with less cost to reach the therapeutic goal when compared to pravastatin, fluvastatin and simvastatin.[63] In a cohort study it was found that rosuvastatin 10 mg is the most effective choice for diabetic patients with dyslipidemia.[64]

Conclusion

The health care professionals looks forward for the imminent future of statins which have wide health outcomes. The improved understanding of long term effects of commonly used statin can considerably reduce accumulating drug induced complications in hospitals. Further more evidence and pharmacoeconomics studies should be conducted for improved decision making and effective health management.

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