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Medical Bulletin

EXCEL Division of Blue Cross Laboratories

PLEIOTROPIC EFFECTS OF STATINS

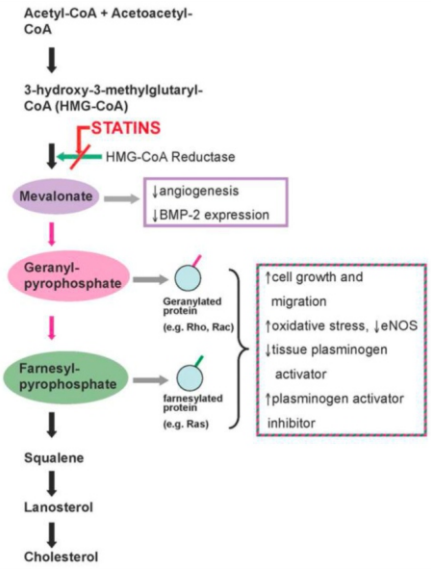
HISTORY OF STATINS

In 1976, a Japanese microbiologist, Akira Endo, first discovered natural products with a powerful inhibitory effect on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, with the possibility of it inhibiting the rate limiting step in the cholesterol biosynthesis pathway, thus having lipid lowering properties.

Apart from the lipid lowering action, few pleiotropic actions have also been widely studied.

MECHANISM OF ACTION OF STATINS

Statins target the hepatocytes and inhibit HMG-CoA reductase, the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor. They alter the conformation of the enzyme when they bind to its active site. This prevents HMG-CoA reductase from attaining a functional structure.

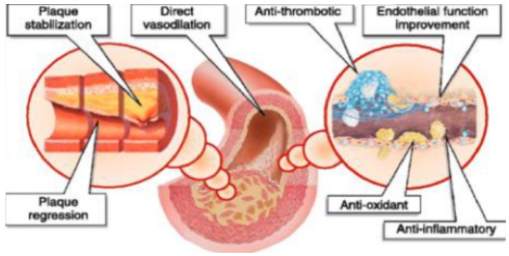


Mechanism of Action of Statins

The mevalonate pathway yields a series of isoprenoids which are vital for diverse cellular functions, from cholesterol synthesis to the control of cell growth and differentiation and hence, HMG-CoA reductase inhibition has many beneficial pleiotropic effects that significantly reduce the incidence of coronary events, both in primary and secondary preventions.

STATINS AND THE CARDIOVASCULAR SYSTEM

Cardiovascular benefits of statins have been conventionally attributed to its cholesterol lowering effects. However, sub analyses of large clinical trials have suggested various other mechanisms as well.



Pleiotropic Effects of Statins

PLAQUE STABILIZATION

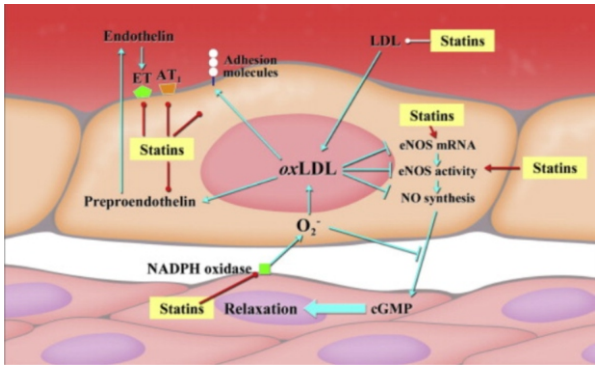
Most acute coronary events occur due to disruption of unstable atherosclerotic plaques, resulting in thrombotic occlusion. These vulnerable lesions are characterized by a lipid-rich core and excessive number of activated inflammatory cells. Macrophages release matrix **metalloproteases** that degrade plaque matrix connective tissue, weaken the fibrous cap, and render them susceptible for rupture.

Statins have been shown to **decrease the levels of these metalloproteases**, oxidized-LDL, core lipid content, and macrophages and to increase collagen content in plaque matrix, actions that increase plaque stability.

ENDOTHELIAL FUNCTION

This effect is mediated by the **inhibition of small molecular weight G-proteins** which are involved in cell proliferation, differentiation, apoptosis, migration, contraction, and regulation of gene transcription.

Statins, by inhibiting isoprenylation (addition of hydrophobic molecules), effectively lower the membrane levels and activity of these proteins and thus improve vascular function.



Effect of Statins on Endothelial Function

Statins also modulate the release and action of vasoconstrictors (endothelin and angiotensin II), especially endothelin-1 (ET-1), which is a powerful vasoconstrictor and hence, decreasing its levels potentially reduces vascular resistance and improves blood flow in coronary and systemic vascular beds.

ANTI-INFLAMMATORY ACTION

The vascular inflammatory response is a complex process that leads to thrombus formation, angiogenesis, neointimal thickening, and atherosclerosis.

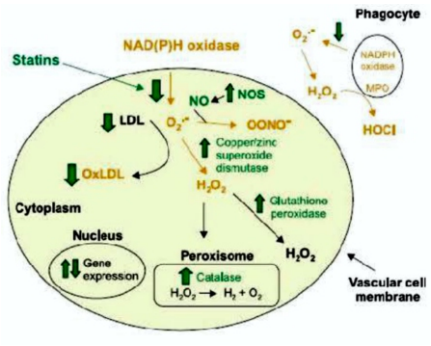
Cytokines, in addition to enhancing cellular adhesion, promote chemotaxis and stimulate vascular proliferation.

Statins inhibits the receptor-dependent activation, mediate the suppression of cytokine and adhesion molecule and help in attenuating the inflammatory process and the consequent impact on CVD risk reduction.

OXIDATIVE STRESS

In several studies, various statins have been shown to:

- Inhibit the uptake and generation of ox-LDL.
- Attenuate vascular and endothelial superoxide anion formation by inhibition of NADH oxidases via Rho-dependent mechanisms.
- Preserve the endogenous antioxidants such as ubiquinone and glutathione in LDL particles.

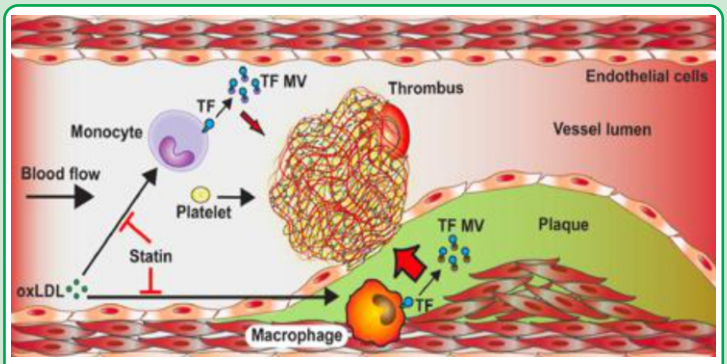


Antioxidant effects of statins

Thus, statins not only decrease the oxidants but also restore the antioxidants, thereby possibly reducing the level of oxidative stress in the vascular milieu.

THROMBOSIS

Statins have been shown to play a role in altering the levels of several key elements in the process of thrombosis. Different statins have varying effects on prothrombotic factors, such as tissue factor, tissue factor pathway inhibitor, platelet aggregation, blood and plasma viscosity, fibrinogen, plasminogen activator inhibitor 1 (PAI-1), and lipoprotein A.



Role of Statins in Prevention of Thrombosis

Statins normalize thrombin generation in hypercholesterolemic patients and reduce platelet aggregation.

Furthermore, decrease in platelet aggregation may be because of reductions in the cholesterol to phospholipid content in the platelet membrane.

CONCLUSION

The benefits of statins may be more far-reaching than previously thought and their potential may extend way beyond cholesterol lowering, with other beneficial, non-cholesterol lowering effects that can prevent cardiovascular events.

Source: The J of Clin Endocrinology & Metabolism 2002; 87(4): 1451-1458; Heart Views 2011; 12(3): 121-127; A. J Cell mol Med 2001; 5(4): 378-387.

HOW DOES EXERCISE AFFECT THE GUT MICROBIOME?

Microbial diversity is essential for health

Diversity is a key parameter for measuring microbiome health, and this ecosystem is made up of hundreds of species. A diverse microbiota profile is associated with enhanced vitamin and short-chain fatty acid (SCFA) production, dietary fibre metabolism and even increased disease protection.

What can exercise do for microbiome?

Recent studies suggest that exercise has a number of benefits for the gut microbiota. It is linked to increase in the number of beneficial microbial species and enriching microbial diversity as well as enhanced SCFA synthesis esp. butyrate and carbohydrate metabolism. Exercise can enhance the number of beneficial microbial species, enrich the microflora diversity, and improve the development of commensal bacteria. All these effects are beneficial for the host, improving its health status.

These organic acids (SCFA) are absorbed through the regional mucosae of the digestive tract and have been shown to modulate host energy homeostasis through interactions between chemosensory cells, which maintain its integrity, reduce inflammation and prevent toxins and metabolites from crossing into the bloodstream.

Exercise can enhance the number of beneficial microbial species, enrich the microflora diversity, and improve the development of commensal bacteria. All these effects are beneficial for the host, improving its health status.

Source:https://atlasbiomed.com/blog/how-does-exercise-affect-gut-microbiome

PPIs AND KIDNEY DISEASE

INTRODUCTION

Proton pump inhibitors (PPIs) are the most commonly prescribed class of medication for the treatment of heartburn and acid-related disorders.

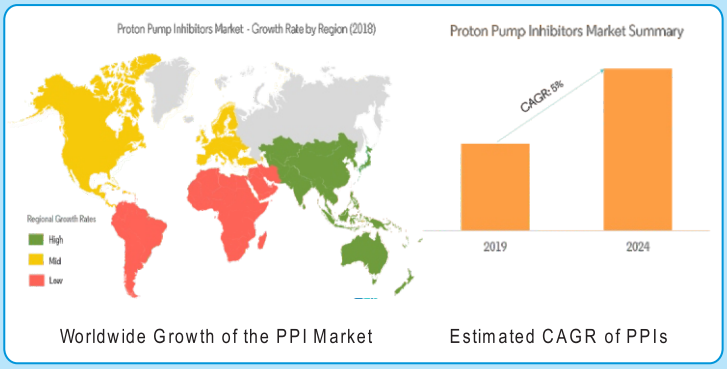
They were clinically introduced more than 25 years ago and have since proven to be invaluable, safe, and effective agents for the management of a variety of acid-related disorders.

Since the introduction of omeprazole in 1989, PPIs have steadily become the mainstay in treatment of acid-related disorders, especially GERD. As compared to the earlier agents such as histamine 2-receptor antagonists (H2RAs), synthetic prostaglandin analogs, & anticholinergics, PPIs have demonstrated consistent patient tolerance, excellent safety, & generally superior acid suppressing capability than prior agents.

GROWTH OF THE PPI MARKET IN INDIA

With the changes in lifestyle factors and importantly psychological factors, which are important risk factors in the development of GERD, its prevalence in India is estimated to be 7.6-18.7%.

The major factors for the growth of the PPI market include this increasing prevalence of GERD.



Worldwide Growth of the PPI Market | Estimated CAGR of PPIs

ASSOCIATION OF PPI USE AND KIDNEY DISEASE

Recent studies have raised concerns over a potential increased risk of kidney problems among PPI users. However, the results of the studies have been inconsistent and hence, it is important for the medical professionals to understand the studies in order to address patient concerns, if any.

HOW DO PPIs AFFECT THE KIDNEYS?

Studies that establish the relationship of PPI use and chronic kidney disease have postulated that the association is likely mediated by the occurrence of intervening acute kidney injury.

Acute interstitial nephritis (AIN), characterised by the infiltration into the interstitium of the kidney tubules by inflammatory cells probably due to an immune-mediated hypersensitivity reaction, which can progress to acute kidney failure, has also been indicated in rare cases with long term PPI use.

Apart from this, hypomagnesaemia has been associated with long term PPI therapy.

RISK BENEFIT RELATIONSHIP BETWEEN PPIs AND KIDNEY DISEASE

Recent meta-analyses has shown the association between exposure to PPIs and risk for CKD or ESRD and it was found that any use of PPIs could be associated with a relative increase in risk for CKD/ESRD.

However, they have shared the limitations of studies and have stated that, it is an association, not proof of a causal relationship.

Patients who use PPIs differ at baseline than those who do not. This basically refers to the use of multiple drugs (poly pharmacy) as well as other multiple underlying conditions. Hence, it becomes difficult to isolate the connection between PPIs and development of kidney disease and various other factors need to be evaluated.

Use of other medications as well as to other underlying conditions, and either of these may be nephrotoxic and not the PPI alone. Also, large retrospective studies have been unable to completely adjust for these baseline differences.

Thus, the medical professional needs to account for these differences before evaluating the role of PPI in the progression of kidney disease.

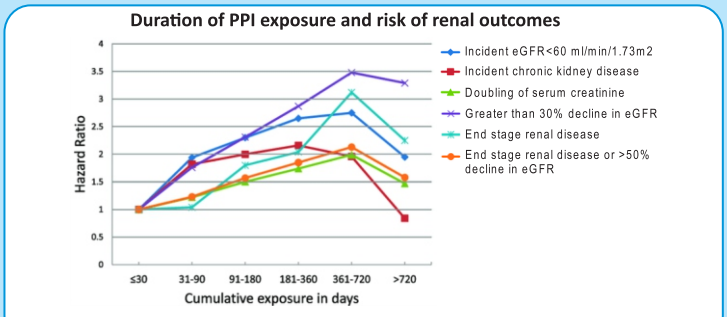
HOW TO DEAL WITH THIS DILEMMA REGARDING PPI USE?

It has become a growing concern with the medical professionals as well as patients regarding the safety of use of PPIs.

However, medical professionals should continue to prescribe PPIs when the benefits of PPIs outweigh the risks and its need be periodically reassessed.

The underlying conditions that may lead to the development of kidney disease also need to be carefully evaluated and the risks effectively communicated.

The following steps can be followed in order to make sure that PPIs are safely used and without any concerns form the patients.



Types of Renal issues with different durations of PPI use

Inform patients that, while studies do raise some concern about long-term PPI use and the potential contributions to kidney disease, it does not show that PPI use cause kidney disease and no decisions should be made in haste as a reaction to this study.

Reassure patients that the benefits of using PPIs often outweigh the possible risks. Let them know that you prescribed a PPI for a clear-cut indication, in the lowest possible dose, and for an appropriate period of time.

Recommend that patients also consider lifestyle modifications that may reduce or eliminate the need for PPIs for long term use.

In conclusion, various safety concerns have been brought up regarding the use of PPI & its association with the development of kidney disease, but it is imperative that one understands this in detail, evaluate the baseline differences between the patients, their underlying conditions, & the existing list of medications & their side effects, weigh out the risks & benefits & prescribe the drug effectively as per its need.

Source: Gut Liver 2017; 11(1): 27-37; BMC Res Notes 2018; 11:448; mordorintelligence.com/ industry -reports/proton-pump-inhibitors-market; Official J of the Int Soc of Nephrology 2017; 91(6): 1482-1494; World J Gastroenterol 2017; 23(37): 6907-6910; The Pharmaceutical Journal 2013; Xie Y etv al. JASN 2016; 27(10): 3153-3163; American Gastroenterological Association (AGA) 2017.

VITAMIN B_{12} AND HYPERHOMOCYSTEINEMIA

INTRODUCTION

Elevated levels of circulating homocysteines (HCys) increases the risk for developing atherothrombotic coronary artery disease (CAD), hypertension, peripheral vascular disease, myocardial infarction (MI), and stroke.

HOW IS HOMOCYSTEINE METABOLISED?

Homocysteine is a sulphur amino acid whose metabolism stands at the intersection of two pathways:

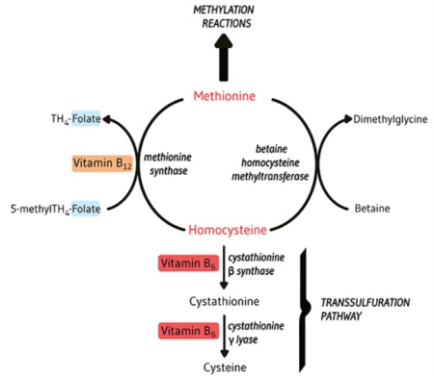
- **Re-methylation** to methionine by the enzyme methionine synthase, which requires folic acid and vitamin B12.
- **Trans-sulfuration**, where HCys combines with serine to form cystathione, which requires vitamin B6.

The two pathways are coordinated by the enzyme S-adenosylmethionine (SAM).

These processes control the levels of HCys in the blood. An imbalance in this metabolism due to various factors causes hyperhomocysteinemia, which has various pathological implications.

WHAT IS HYPERHOMOCYSTEINEMIA?

Hyperhomocysteinemia is a medical condition characterized by an abnormally high level of homocysteine in the blood, conventionally described as > 15 µmol/L.



Homocysteine Metabolism

Mean HCys levels increase throughout life by 3-5 µmol/L and this level is higher in men than in women. Moreover, each 5 µmol/L increase in HCys is associated with increased risk of vascular arteriosclerotic disease.

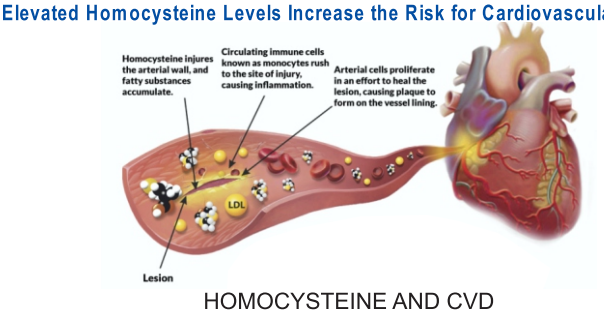
The increase in the plasma levels of HCys may be caused by several factors such as genetic polymorphism, deficiency of cofactor(s). Other factors include age & gender, genetics, vitamin status, lifestyle and ageing, etc.

Folic acid, vitamin B12 and pyridoxine are known to be essential co-factors in HCys metabolism and it has been well established that, deficiency of these is the dominant cause of hyperhomocysteinemia.

WHAT ARE THE IMPLICATIONS OF HYPERHOMOCYSTEINEMIA IN CARDIOVASCULAR DISEASE?

There is a significant correlation between hyperhomocysteinemia and CVD. It is believed that hyperhomocysteinemia leads to endothelial cell damage, reduction in the flexibility of vessels, and alters the process of haemostasis.

Hcys is known as an independent risk factor for atherosclerosis, and the presumed mechanisms of these effects include an increase in proliferation of vascular smooth muscle cells, endothelial dysfunction, oxidative damage, an increase in synthesis of collagen and deterioration of arterial wall elastic material.



HOMOCYSTEINE AND CVD

It has been demonstrated that HCys is capable of initiating an inflammatory response in vascular smooth muscle cells by stimulating CRP production.

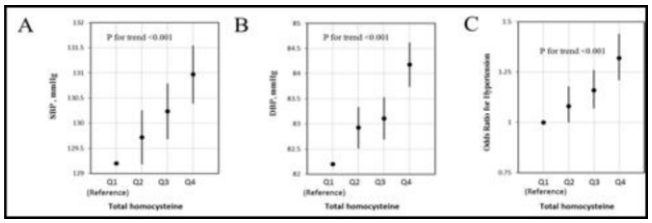
Hyperhomocysteinemia has also been shown to be associated with a higher risk of venous thrombosis. Increased HCys levels have shown a predilection towards promotion of platelet adhesion to endothelial cells and have also been associated with higher levels of prothrombotic factors which lead to the augmentation of thrombus formation.

HYPERHOMOCYSTEINEMIA AND HYPERTENSION

It is a universal truth that high blood pressure or hypertension leads to CVD. The main proposed mechanism is through homocysteine mediated damage to vascular smooth muscle and endothelial cells. This damage, in turn, leads to a loss of arterial vasodilation, vascular integrity, and thus increased blood pressure (BP) and accelerated atherosclerosis.

Hcys has been positively associated with both diastolic & systolic blood pressure. In case of HCys concentration increase of 5 µmol/L, diastolic & systolic blood pressure in men increased by 0.5 and 0.7 mmHg, respectively and in case of women, the correlation of HCys & blood pressure was stronger, with 0.7 and 1.2 mmHg increase in diastolic and systolic blood pressure, respectively.

The graphs below indicate that, with an increase in the plasma HCys concentrations to the levels of the 4th quartile, there is a consistent rise in the systolic as well as the diastolic blood pressure thus increasing the odds ratio for developing hypertension.



Increased prevalence of hypertension through different levels of plasma HCys
Q1 (<10.1 µmol/L), Q2 (10.1 to <12.2 µmol/L), Q3 (12.2 to <14.9 µmol/L), Q4 (14.9 µmol/L)

WHAT IS THE ROLE OF VITAMIN B IN THE MANAGEMENT OF HYPERHOMOCYSTEINEMIA?

Normal HCys metabolism is dependent upon adequate stores of three dietary vitamins: folic acid, vitamin B12 (mecobalamin), and vitamin B6 (pyridoxne).

- Folic acid is a substrate for cellular production of tetrahydrofolate (THF), a precursor to 5-methyl-THF that is required for normal methionine synthase enzyme activity.
- Mecobalamin is a key cofactor required for normal methionine synthase activity.
- Pyridoxine phosphate is a cofactor necessary for normal cystathione B synthase (CBS) enzyme activity.

They are an integral part of HCys metabolism and adequate levels of these vitamins help keep the HCys levels in the blood under control.

CONCLUSION

The identification of HCys as a risk factor for CVD & hypertension carries important public health implications. If effective, the simplicity, availability, & presumably the safety profile of this hyperhomocysteinemia treatment of combining folic acid, B6 and B12 vitamins supplementation makes an attractive adjunct to the standard medical therapy for CVD.

Source: Ann rev Med 2009; 60: 39-54; Bioinformation 2013; 9(4): 193-196; Ann Rev Nutr 1999; 19: 217-246; The J of Clin Hypertension 2017; 19(11): 1171-1172; Nutr J 2015; 14: 6; Clin Rheumatology 2007; 26(5): 739-742; BMJ Open 2018; 8: e021103;

For More Information: **Dr. Prabhu Kasture** (MD, DPH), GM- Medical Services. **Call:** 022 66638043 **e-mail:** prabhu.k@bluecrosslabs.com **Correspond:** Blue Cross Laboratories Pvt Ltd. Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013

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