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Medical Bulletin

EXCEL Division of Blue Cross Laboratories Pvt Ltd.

ASSOCIATION OF LIPOPHILIC STATINS IN CANCER PREVENTION

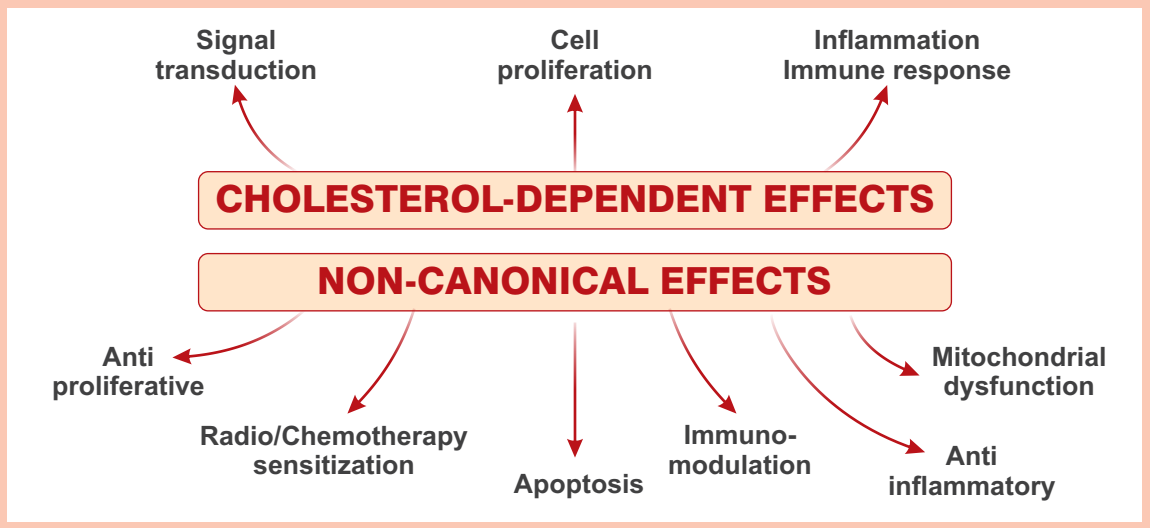
Cancer remains a global health challenge, accounting for some 10 million deaths per year worldwide. Despite substantial advancements in prevention and treatment, cancer remains one of the most common causes of mortality, particularly in older adults.

There is a critical, unmet need for more effective primary therapies that can be integrated into current treatment regimens without increasing adverse effects.

Cholesterol plays vital roles in biological processes including cell membrane maintenance, steroid hormone synthesis, vitamin D and bile acid production and the formation of lipid rafts and caveolae that facilitate transport, signal transduction and cell polarization.

In addition, statins impact on isoprenoid biosynthesis can produce diverse pleiotropic effects. Isoprenoids serve as lipid anchors for intracellular signaling proteins essential for cell growth, survival and differentiation. The mevalonate pathway is also limiting for production of isoprenoids, which serve key roles in cellular metabolism and signaling such as isopentenyl diphosphate (IPP), farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP). Modulating isoprenylation can influence cellular signaling pathways, potentially contributing to statins therapeutic benefits. The lipophilic statins, such as simvastatin, lovastatin and atorvastatin, are more bioavailable in the periphery, providing the potential to impact multiple targets of mevalonate metabolism in cancer cells as depicted in the diagram.

Atorvastatin displayed the highest antitumor effect amongst all the lipophilic statins when they were tested against the various cancer cell lines viz. breast, prostate, colon, lung, ovarian, brain and melanoma.



Mechanisms of Action in Cancer Prevention

1. **Inhibition of HMG-CoA Reductase:**
   - Reduces production of mevalonate, a key precursor not only in cholesterol synthesis but also in the synthesis of isoprenoids.
   - Isoprenoids are critical for the post-translational modification of proteins like Ras and Rho, which are involved in cell proliferation and survival -common pathways in cancer development.

2. **Anti-inflammatory Effects:**
   - Chronic inflammation is a known risk factor for cancer.
   - Atorvastatin downregulates inflammatory cytokines (e.g., IL-6, TNF-α) and CRP, potentially reducing cancer-promoting inflammation.

3. **Pro-apoptotic and Anti-proliferative Effects:**
   - Promotes apoptosis (programmed cell death) in cancer cells.
   - Inhibits cell proliferation in various types of tumors (e.g., breast, prostate, colon) by affecting signaling pathways like Akt, MAPK, and NF-κB.

4. **Anti-angiogenic Properties:**
   - Reduces formation of new blood vessels in tumors by lowering VEGF and other angiogenic factors.
   - Starves tumors of nutrients and oxygen.

5. **Immunomodulation:**
   - May enhance immune surveillance by improving antigen presentation and T-cell response.

Observational studies performed on patients who used statins for different pathologies, revealed that statins reduced the risk of developing various cancers, and improved the outcomes for cancer patients. Studies have shown that there is a direct correlation between statin use and a reduced risk of cancer onset, or improvement in cancer outcomes. Currently, there are many ongoing clinical trials aimed at exploring the potential of statins to lower the mortality and the disease-recurrence risk. All these results are the foundation of new treatment directions in cancer therapy. In conclusion, the strong biologic rationale and observational studies supporting the effect of statins as prevention therapy for several cancers suggest that additional investigation of statins may be warranted.

Source: *World J Clin Oncol. 2020 Aug 24;11(8):573–588; Front. Pharmacol., 07 July 2023.*

BIDIRECTIONAL ASSOCIATION BETWEEN GASTRO ESOPHAGEAL REFLUX DISEASE AND HYPERTENSION

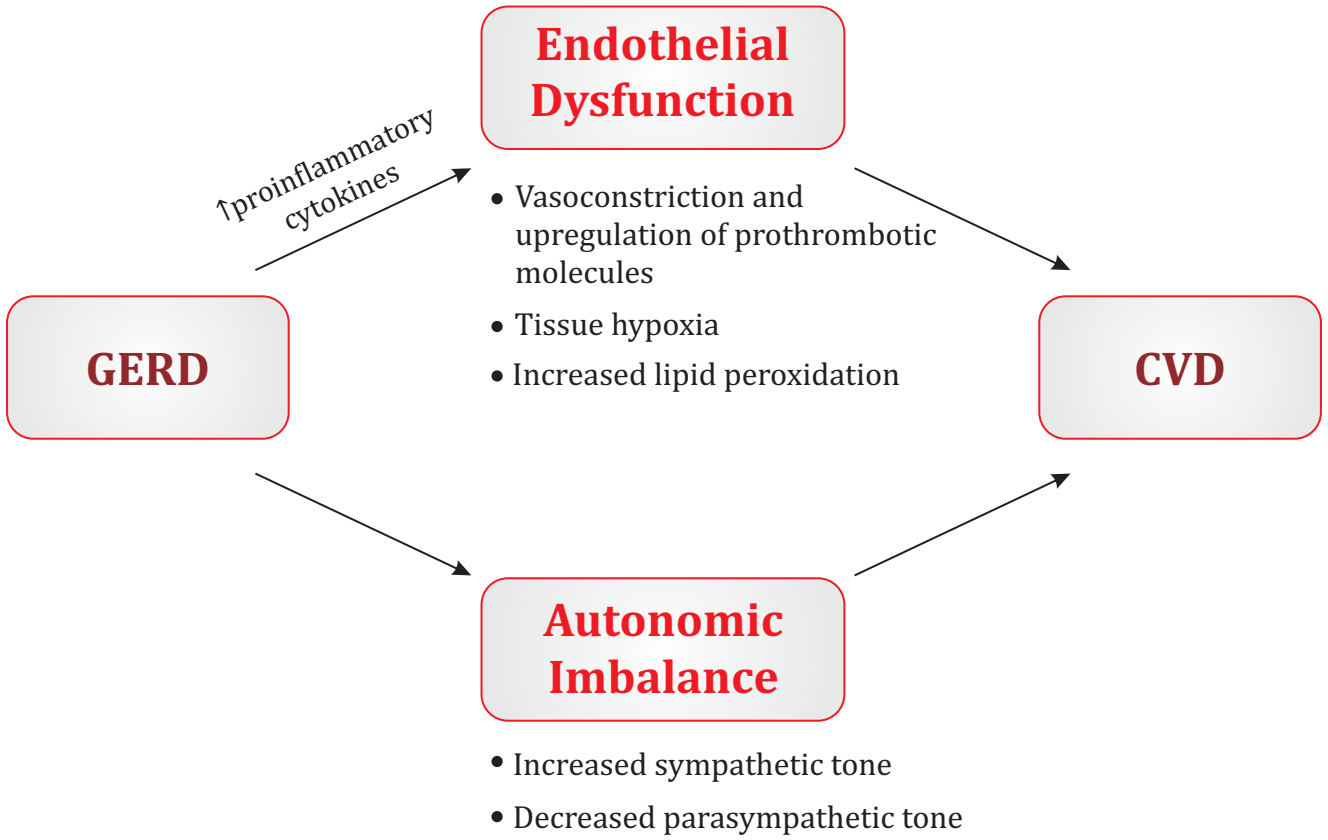
Gastroesophageal reflux disease (GERD) is characterized by the reflux of gastric contents into the esophagus, oral cavity (including the pharynx), and/or lungs, resulting in various symptoms, end-organ effects, and potential complications. The most common symptoms of GERD include heartburn and acid reflux. GERD is primarily classified into erosive esophagitis (EE), non-erosive reflux disease (NERD), and Barrett's esophagus. The global weekly prevalence of GERD symptoms is approximately 13%, with rates in Asian countries ranging from 5% to 10%, with recent data indicating increasing prevalence worldwide.The incidence of GERD has increased in recent years. A potential association between HTN and GERD patients was found. Shared mechanisms, including systemic inflammation, oxidative stress, and lifestyle factors, appear to play a key role in their coexistence. There are many mechanisms underlying its pathogenesis.

Notably, patients with GERD displayed significantly higher nocturnal blood pressure compared to those without it. Acid suppression therapy resulted in significant reductions in both esophageal monitoring parameters and blood pressure parameters in patients with reflux esophagitis demonstrating a significant association between hypertension and GERD, suggesting that acid suppression therapy not only restores normal esophageal pH but may also help maintain normotension.

Several potential pathophysiological mechanisms may explain the association:

1. The vagus nerve affects esophageal peristalsis, the function of the lower esophageal sphincter, and gastric motor function. The autonomic nervous system plays a crucial role in controlling blood pressure levels too. Excessive activation of the sympathetic nervous system may elevate blood pressure through mechanisms such as cytokine imbalance, activation of the renin-angiotensin system, abnormal cardiopulmonary reflexes, and dysregulation of pressure receptors.
2. Disturbances in gastrointestinal microbiota activate inflammatory pathways that contribute to esophageal mucosal injury. Such disturbances are associated with reduced lower esophageal sphincter resting pressure and delayed gastric emptying. Intestinal microbiota may influence visceral neuromodulatory mechanisms along the “microbiota-brain-gut axis”, potentially contributing to the development of visceral hypersensitivity. Intestinal dysbiosis can contribute to the development of hypertension through inflammatory factors, short-chain fatty acids (SCFAs), and lipopolysaccharides (LPS). Additionally, the direct infiltration of microbial components into vascular tissue may mediate inflammatory responses and dyslipidemia, which are relevant to atherosclerosis progression.
3. Nitric Oxide (NO) plays a crucial role in regulating lower esophageal sphincter (LES) pressure, and a reduction in NO can lead to decreased LES pressure, thereby contributing to the development of esophageal reflux. Abnormal NO levels may interfere with signaling pathways leading to disturbances in the epithelial barrier, exacerbated inflammation, and accelerated transformation of the esophageal columnar epithelium. The impact of NO on both esophageal function and blood pressure is substantial.

4. Patients with a history of hypertension frequently take medications such as calcium channel blockers (CCBs), β-blockers, and antiplatelet drugs. These medications can damage the esophageal mucosa, reduce the tension of the lower esophageal sphincter, contribute to the formation of the esophageal hiatus, and in some cases, lead to the development of a hiatal hernia, thereby exacerbating reflux. This mechanism may play a significant role in the pathogenesis of gastroesophageal reflux disease.



GERD is a potential risk factor for HTN, with GERD patients demonstrating an elevated likelihood of developing HTN highlighting shared inflammatory and metabolic pathways. The key contributors include autonomic nervous system dysfunction, chronic inflammation, and oxidative stress. Thus, hypertensive individuals should be evaluated for GERD symptoms to enhance treatment effectiveness and vice versa.

Source: *Journal of Inflammation Research 2025:18; JGH Open. 2025 Apr 12;9(4):e70158.*

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