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BLUGLIP (VILDAGLIPTIN) TREATS HYPERTENSION BY MODULATING SERUM VEGF LEVELS

The prevalence of type 2 diabetes mellitus (T2DM) is constantly increasing at an alarming rate with which it confers an excess risk for a wide range of vascular diseases such as arterial stiffness, hypertension and atherogenesis. Hypertension and T2DM are common co-morbidities and is twice as frequent in patients with diabetes as compared with non-diabetics.

The pathophysiology of hypertension in diabetes involves various mechanisms:

- **Maladaptive changes in the autonoimic nervous system**
- **Vascular endothelial dysfunction arterial stiffness**
- **Enhanced activation of renin-angiotensin-aldosterone system (RAAS)**
- **Immune function alterations**
- **Harmful environmental factors**

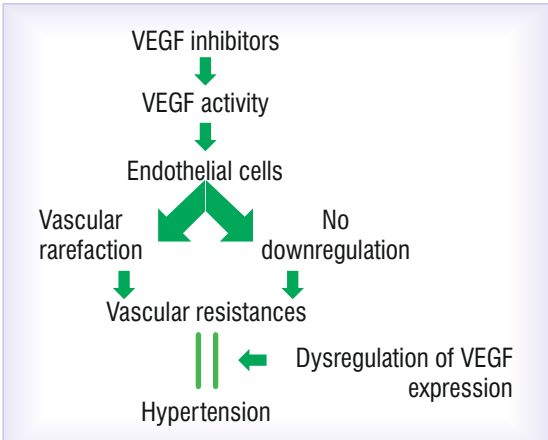
Diabetes may enhance arterial stiffness through pathological changes in the vascular bed such as reduced nitric oxide (NO) bioavailability, increased oxidative stress, chronic low-grade inflammation, increased sympathetic tone and changes in the type or structure of elastin and/or collagen in the arterial wall.

With increasing arterial stiffness, the stiffness in the central arteries become more pronounced than the peripheral artery stiffness. This occurs mainly due to the disruption in the normal architecture of the collagen and the elastin fibers within the arterial layers. This pathological change is triggered by many factors, one of the main being Advanced glycation end-products (AGE products) that are produced with high blood sugar levels. The deformed elastin fibers are more prone to calcification which contributes to arterial stiffness.

The increased arterial stiffness leads to an increase in systolic arterial pressure which in turn increases the shear stress on the arterial wall triggering the pathological changes and creating a vicious cycle.

Role of vascular endothelial growth factor (VEGF) in hypertension:

Normally, binding of VEGF to its receptors leads to activation of multiple pathways including the endothelial nitric oxide (eNOS) pathway that leads to increased NO production and vasodilation. Hence, when the VEGF pathway is inhibited, the NO pathway is suppressed and endothelin-1 pathway is stimulated, promoting vasoconstriction and consequent hypertension. The subsequent diminution of the microvascular surface area leads to an increase in peripheral vascular resistance and a resultant increase in blood pressure. This is known as microvascular rarefaction.



Action of Vildagliptin on VEGF levels

It was observed that Vildagliptin had the ability to modulate the blood pressure via maintaining high serum VEGF levels providing a protective action on the vasculature through its ability to promote angiogenesis and endothelial homeostasis.

Hence, it can be concluded that Vildagliptin plays an important role in treating hypertension in type 2 diabetic patients via its action of maintaining the VEGF levels, thus preserving the integrity of the blood vessels as well as via angiogenesis and overall maintaining endothelial homeostasis. It can therefore be considered as a choice of drug for treating these two common co-morbidities that usually exist together.

Source: Wicinski M et al. Int J of Mol Sciences 2020; 21(7): 2275; www.ncbi.nlm.nih.gov/books/NBK279027,Tian X et al. Hypertension 2022; 79: 1487-1496; El-Naggar RA et al. J of Cardiovasc Pharmacology Ther 2019; Maki-Petaja KM et al. Hypertension 2021; 17: 1591-1599; De Oliveira Alvim R et al. Diabetology & Metabolic Syndrome 2013; 5(45); Rudnika ML et al. Folia cardiologia 2022; 17(4): 243-250.

STATINS [LIPONORM] AND ITS ASSOCIATION WITH REDUCED RISK OF OSTEOPOROTIC FRACTURES

Osteoporosis is a common metabolic disorder characterized by a reduced bone mineral density (BMD) induced by an imbalance in osteoblastic and osteoclastic bone formation and resorption which result in bone weakening and fracture injuries.

This is a major healthcare problem among the elderly. Osteoporosis and low bone mass affect almost 80% of elderly women, as well over 40% of elderly men. Globally, it is estimated that one in three women and one in five men over the age of 50 suffer from osteoporotic fractures.

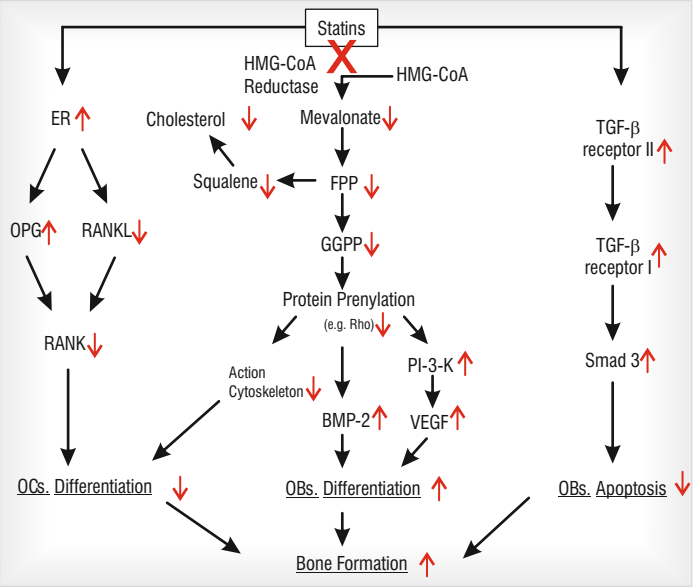
Statins are known for their beneficial effects on cardiovascular diseases. Bisphosphonates inhibit an enzyme in the mevalonate pathway giving rise to the hypothesis that statins could also be beneficial in pathologies related to loss of bone mass, while reducing the potential for later osteonecrosis.

Mechanisms of statins for new bone formation

Statins have multi beneficial actions on bone repair by different mechanisms. They increase new bone formation by promoting osteogenesis, suppressing osteoclastogenesis, inhibiting osteoblast apoptosis.

Statins induced osteogenesis/osteoblastic differentiation

Statins inhibit HMG-CoA reductase, and thereby block conversion of HMG-CoA to mevalonate. Downstream products of mevalonate [e.g., farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP)] are regulated by statins. During statins-induced osteoblast differentiation, FPP and GGPP decreases. Expression of the exogenous FPP blocks differentiation of the osteoblastic cells. This indicate that indicate that statins induce osteogenesis by reducing FPP and GGPP levels. On the other hand, FPP and GGPP are of vital importance for post-translational lipid modification (prenylation) of certain GTP binding proteins (e.g. Rho), which gets activated after prenylation. Thus, statin-induced suppression of FPP or GGPP might impair protein prenylation by increasing the expression of bone morphogenetic protein-2 (BMP-2). Another consequence of the inhibition of protein prenylation is the increased expression of VEGF via the increased production of phosphatidylinositol 3 kinase (PI3-K).



Statin-inhibited osteoblast apoptosis

Statins may also increase bone formation by inhibiting osteoblast apoptosis through the transforming growth factor beta (TGF-β)/mothers against decapentaplegic homolog 3 (Smad3) signaling pathway which is crucial for the preservation of bone mass. TGF-β plays a critical role in bone formation and Smad proteins are key components of the TGF-β signaling pathway.

Statin-suppressed osteoclastogenesis

The osteoprotegerin (OPG)/receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK system is the final mediator in the regulation of osteoclastogenesis and it plays an essential role in the proliferation and differentiation of osteoclasts. Anti-osteoclastic effect of statins is due to their effect on the OPG/RANKL/RANK signaling pathway. On the other hand, estrogen receptor (ER) also play an important role in the inhibition of osteoclastogenesis. Estrogen can reduce RANKL and further lead to the inhibition of osteoclastogenesis.

Clinical Evidences

Several studies (pre-clinical & clinical) have investigated the effect of statins on the occurrence of osteoporosis and have confirmed the above mechanisms.

- A recent study (year 2023) in elderly patients (n=365,656) found that statin use associated with significant reduction in the risk of osteoporotic fractures in this population.
- Meta-analysis (33 trails, 16, 63,665 patients) concluded that statin treatment had a tendency towards a positive effect on the reduction of fracture risk and marked improvement of bone mineral density (BMD) in statin-treated patients (n=314,473). These results are in line with another large meta-analysis conducted in Taiwan, including 45342 patients - statin users and 115594 patients - statin non-users.
- A nested case-control study in patients (n=17,041) with metabolic syndrome (≥50 years) supported the beneficial role of statins on major osteoporotic fractures, especially vertebral fractures.
- A population-based case–control study (n = 3675) found that women older than 60 years on statins for over 2 years had 52% reduced risk of non-pathological fracture compared to women not on statins.
- According to several observational studies ***lipophilic statins*** like ***Atorvastatin*** rather than hydrophilic statins was found to have better outcomes for osteoporotic fractures due to differences in their polarity and bone bioavailability. This is because only the lipophilic statins predominantly induce bone BMP-2 expression, which promotes differentiation of mesenchymal stem cells into differentiated osteoblasts and bone formation.

Source: Zhang Y, et al. Pharmacol. Res. 2014; 88: 53-61, Salari N, et al. J. Orthop. Surg. Res. 2021; 16(1): 1-20, Seo DH, et al. Osteoporos Int. 2023, Leutner M, et al. Ann Rheum Di. 2019;78:1706–11, Kim KJ, et al. J Lipid Atheroscler. 2021;10 (3):322-333

PPIs IN MANAGING LARYNGEAL DISORDERS

Gastric reflux disease is a GI motility disorder that results from the reflux of the gastric juice into the esophagus. However, many times this reflux is not restricted to the esophagus and can affect other organs like the larynx. The presence of extraoesophageal reflux disease has an overall effect on the health-related quality of life. It is important to note that fewer than 40% of Laryngopharyngeal reflux disease (LPRD) patients report typical symptoms of GERD such as heartburn. Other symptoms are breathing difficulties and voice changes.

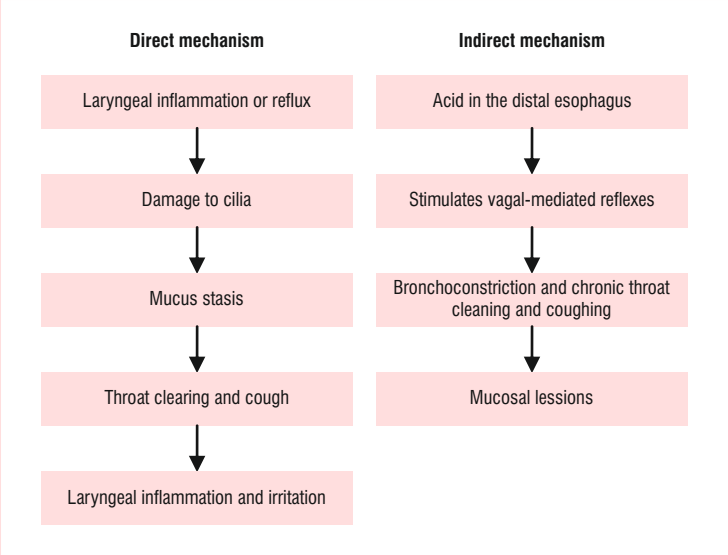
GERD can be divided into extraesophageal reflux, atypical reflux, laryngopharyngeal reflux (LPR) and reflux laryngitis.

LPRD is caused by the backflow of the stomach contents and/or gastric acid into laryngopharynx. The damage to the laryngeal mucosa may be the result of the gastroduodenal contents whether chronic or due to an acute incident.

PATHOPHYSIOLOGY OF LPRD

Two hypotheses exist as to how gastric acid precipitates extraoesophageal pathologic response:

- The direct acid-pepsin injury to the larynx and the surrounding tissues via the esophago-pharyngeal reflux.
- The acid in the distal oesophagus stimulates the vagal mediated reflexes resulting in bronchoconstriction and chronic coughing leading to mucosal lesions.
- A combination of these two mechanisms may produce pathologic changes seen in LPR.



The aim of medical management for LPRD is neutralization of gastric juice acidity and enhancement of GI motility. Treatment with proton pump inhibitors (PPIs) is required for resolution of laryngeal symptoms and physical findings in patients with LPRD.

There are 4 categories of drugs that are used in treating LPRD: PPIs, H2 receptor antagonists, prokinetic agents and mucosal cytoprotectants, with PPIs being the mainstay of medical treatment.

It has been observed through various studies that treatment with PPIs for a period of 3 months showed a significant improvement in the symptoms associated with LPRD.

PPI like pantoprazole (20 mg) taken twice daily resulted in significant improvements in LPRD symptoms by 2 months and complete resolution of the same at the end of 6 months. Supporting the earlier findings, a recent study has also revealed a significant improvement in LPRD symptoms at 2 months, 4 months and 6 months of PPI treatment.

Source; Ragaee MA et al. Otolaryngology 2023; 89(10); Makhdoom N et al. Saudi Med J 2007; 28(7): 1068-1071; Joshi AA & Chiplunkar B. Int J Head Neck Surg 2022; 13(1): 8-17; Chiba T et al. Med res Archives 2017; 5(2): 1-14; Bhargava A et al. Ind J Otolaryngol Head Neck Surg 2019; 71(30: 371-377; Osman HA et al. J of Gastroenterology & Hepatology Res 2019; 8(1).

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