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RENOPROTECTIVE EFFECT OF CILNIBLU (CILNIDIPINE) VERSUS L-TYPE CALCIUM CHANNEL BLOCKERS IN HYPERTENSIVE PATIENTS

The relationship of hypertension and renal function is that of a vicious cycle. Uncontrolled hypertension is a risk factor for the deterioration of kidney function and chronic kidney disease itself can have a negative impact on blood pressure which can lead to refractory hypertension.

Sympathetic stimulation in the renal afferent and efferent arterioles increases resistance and decreases renal blood flow. Renal ischemia will cause further sympathetic activation releasing pressor substances like renin and norepinephrine, a sympathetic neurotransmitter, leading to aggravated hypertension.

Therefore, hypertension and chronic kidney disease can cause mutual deterioration.

There are six subtypes of calcium channels namely L, N, P, Q, R and T. Of these the notable ones are the L type calcium channels that are present in the heart and blood vessels and the N type calcium channels that are present in the sympathetic nerve endings which regulates the release of norepinephrine, and in turn controls the renal haemodynamics via the α-adreno receptors that control the blood pressure and via the glomerular filtration rate (GFR).

Calcium channel blockers (CCBs) have been used in the treatment of hypertension, including in patients with diabetes. They are potent vasodilators and are particularly effective in reducing peripheral resistance.

CILNIDIPINE AND RENAL FUNCTION

Increased serum creatinine & decreased eGFR are indicators of damaged renal function. In addition, Urinary protein excretion (UPE) & Urinary protein creatinine ratio (UPCR) are indicative of the urinary protein quantitative diagnosis.

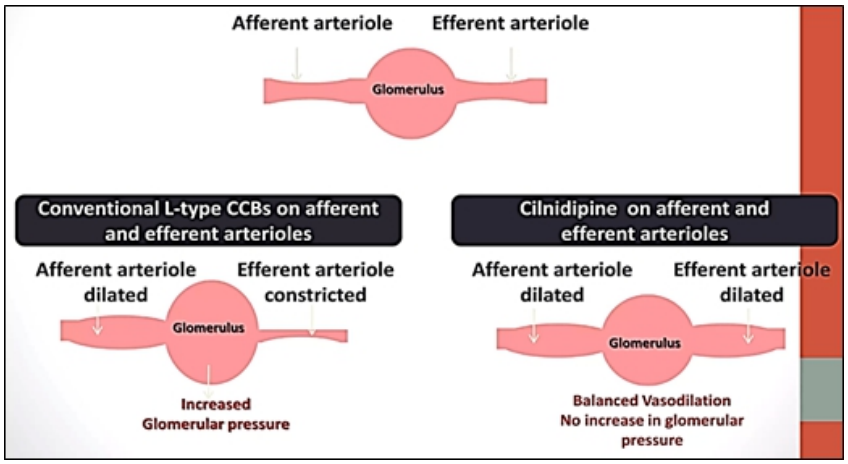
Higher values indicate a protein leak from the renal vessel wall compromising renal function which destroy the Sertoli cells in the glomerulus resulting in glomerular sclerosis.Thus,it is imperative to also control proteinuria along with the blood pressure.

A meta-analysis of 11 studies was carried out to evaluate the beneficial effect of Cilnidipine on the kidney function parameters as compared to L type CCBs like amlodipine. The studies included patients treated for a period of 12-24 weeks and the results on the renal parameters were evaluated as follows.

Effect on serum creatinine	• No significant difference in the serum creatinine was observed between the L type CCB group and the Cilnidipine group.
Effect on UPE	• A significant decrease in the values in the Cilnidipine group was observed especially in patients with CKD and increased protein loss in the urine.
Effect on UPCR	• There was a significant reduction in the UPCR in the group recieving Cilnidipine and on the contrary there was a slight increase in the same in the L type CCB group.
Effect on eGFR	• The patients recieving Cilnidipine showed an increase in the eGFR values whereas the patients recieving L type CCB showed either no change or a decrease in the eGFR.

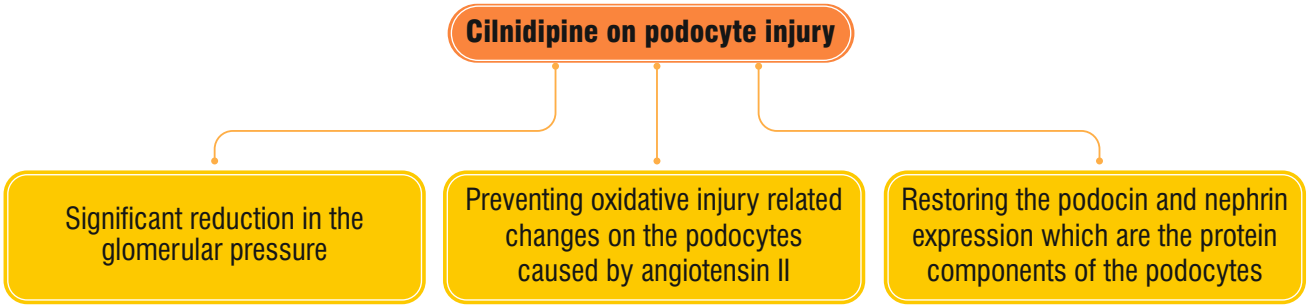
The sympathetic nerves are distributed to all parts of the renal vascular system including the afferent and the efferent arterioles of the glomerulus. The norepinephrine that is released from the N type calcium channel constricts both afferent and efferent glomerular arterioles and hence the inhibitory action of Cilnidipine on the N type calcium channels dilates both the arterioles.

This reduces arteriolar resistance, especially in the efferent arterioles and lowers the intraglomerular pressure thus protecting against glomerular damage.



Another hypothesized mechanism of Cilnidipine being reno-protective is its effect on the podocytes which act as permeability barrier and restrict the passage of large molecules like albumin.

Cilnidipine elicits protective effects against glomerular podocyte injury through multiple mechanisms.



All these protective effects of Cilnidipine put together suppresses the development and progression of overall proteinuria along with beneficial effects on other renal parameters, thus help to protect and preserve the renal function in hypertensive patients.

Source: Srivathsan M et al. Cureus 2022; 14(8): e27847; Konno Y & Kimura K. Int Heart J 2008; 49: 723-732; https://www.who.int/india/news/detail/02-06-2022-india-hypertension-control-initiative--a-high-impact-and-low-cost-solution.

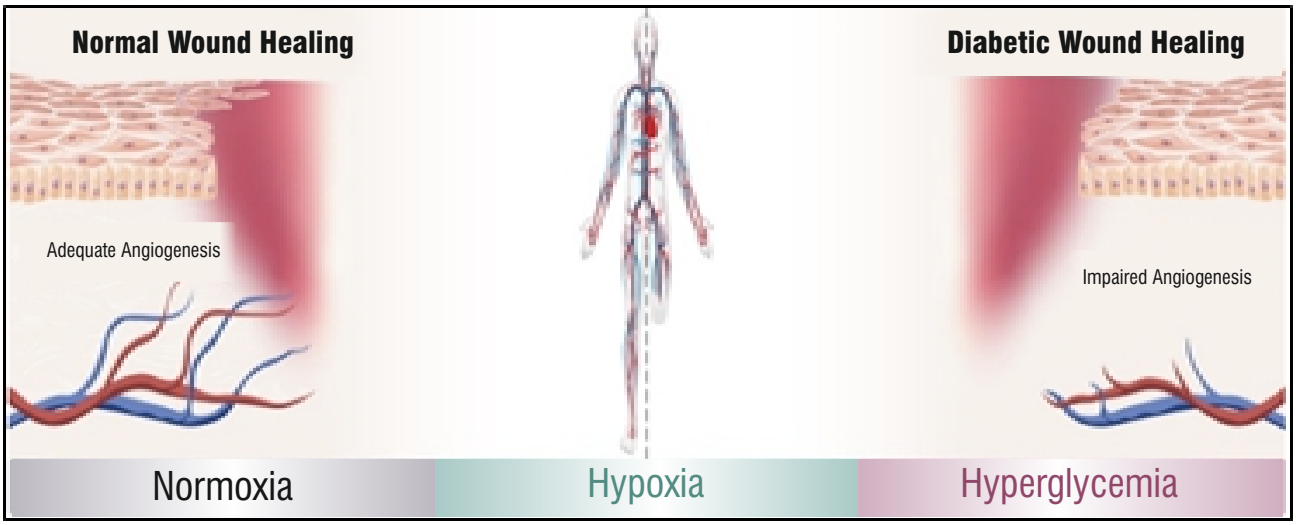
BLUGLIP (VILDAGLIPTIN) & HEALING OF DIABETIC FOOT ULCERS

Diabetic patients are at an exceptionally high risk for poor wound healing, especially with foot ulcers. The risk for developing chronic foot ulcers has been estimated to be 15-20% and they are responsible for a higher number of limb amputations associated with decreased quality of life and increased mortality.

The incidence of lower extremity amputations in patients with diabetes exceeds 20 times that of the normal population and the mortality rate due to the lower extremity amputation is about 13% in the first year.

Diabetes usually impairs the mechanism of normal wound healing at various stages resulting in delayed wound healing leading to peripheral vascular disease and lower limb amputations.

PATHOPHYSIOLOGY OF CHRONIC FOOT ULCERS

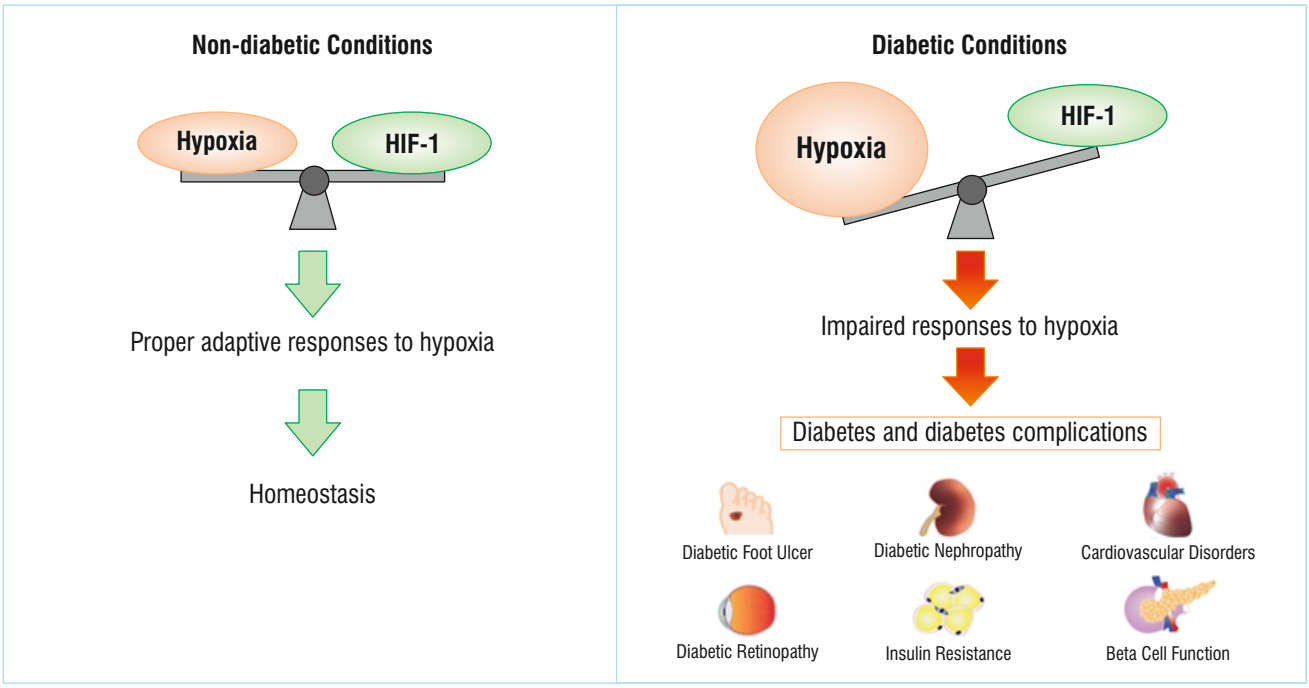


The pathophysiology of chronic foot ulcers is complex and both macro and microangiopathy including neuropathy strongly contribute to the development and delay of diabetic wounds through impaired tissue feeding and response to hypoxia.

A critical stimulus for normal wound healing is relative hypoxia and an impaired response to the same contributes to poor wound healing.

Oxygen plays an important role in wound healing and during an inflammatory process, the wound sites are often hypoxic due to the disruption of the vasculature leading to impaired oxygen delivery causing a rapid influx of inflammatory cells participating in the healing process with high metabolic demands for oxygen.

Adaptive responses of a cell to hypoxia are mediated by hypoxia inducible factor-1 (HIF-1) which is expressed in response to a decrease in cellular oxygen. HIF-1 is a protein that functions as an activator of vascular endothelial growth factor (VEGF) as well as inducible nitric oxide (NO) synthase. The activation of these contributes to limiting the hypoxic injury by promoting angiogenesis and wound healing.



It has been observed that diabetes impairs the HIF-1 and VEGF expression which can be established by observed low levels of HIF-1 in foot ulcer biopsies.

ROLE OF VILDAGLIPTIN IN HEALING OF THE FOOT ULCERS

Dipeptidyl peptidase-4 (DPP-4) inhibitors like vildagliptin have shown to have beneficial anti-inflammatory effects such as reducing oxidative stress and inflammation. It has been suggested that the incretin hormone, glucagon like peptide-1 (GLP-1) causes HIF-1 up regulation and improves VEGF generation by reducing the oxidative stress.

DPP-4 inhibitors promote the recruitment of progenitor cells to the wound area allowing the scaffolding of wounds. It promotes angiogenesis and has widespread effects on optimising the immune response to persistent hypoxia in chronic diabetic wounds.

Neovascularization results from the circulating progenitor and stem cells that differentiate into mature endothelial cells from the migration and proliferation of specialized adhesion endothelial cells (CD-31 positive endothelial cells) from the pre-existing blood vessels. Vildagliptin has the ability to attract these CD-31 positive endothelial cells and accelerate the wound healing process.

It has been observed that the GLP-1 levels increase due to the inhibition of DPP-4 enzyme by inhibitors like vildagliptin in the wound area in order to improve the migration of multiple cells, thus accelerating the wound healing process.

Also, placebo-controlled studies have shown that the HIF-1 and VEGF levels were significantly lower in control diabetic patients as compared to those treated with vildagliptin.

To conclude, vildagliptin treatment improves would healing, especially in patients with diabetic foot ulcers by reducing oxidative stress via enhancing GLP-1 as well as promoting vascularization and angiogenesis via HIF-1 and VEGF and can be considered as a promising anti-diabetic drug in treating patients with chronic diabetic ulcers.

Source: Vangaveti et al. Diabetology & Metabolic Syndrome 2022; 14(183); Lee CH et al. Pharmaceuticals 2022; 15: 1358; Marfella R et al. Exp Diabetes Res 2012; 2012: 892706.

PPIs ON GLYCEMIC CONTROL

Patients with diabetes, especially the ones with a poor glycemic control present with a higher prevalence of gastrointestinal (GI) symptoms.

Proton pump inhibitors (PPIs) are commonly prescribed worldwide for gastroesophageal related disorders. By blocking the H+/K+ ATPase (proton pump), they potently inhibit the gastric acid secretion.

Along with this, they are also known to elevate the levels of gastrin which is considered to be an early incretin candidate as it stimulates β-cells of the pancreas to secrete insulin.

Systemic review and meta-analysis from multiple articles have shown that glycemic control with added PPI therapy was superior compared to standard care.

There were several proposed mechanisms supporting the improved glycemic control with the use of PPIs. One of the stark mechanisms was the gastrin levels which were elevated among the group using PPIs. Gastrin through its incretin like effect, stimulates β-cells to proliferate and secrete insulin thus improving glycemic control.

Additionally, the delayed gastric emptying effect of PPI therapy could also reduce the post prandial glucose levels.

This demonstrates the therapeutic potential of PPI therapy for diabetes management and further exploration is warranted to corroborate the same.

Source: Peng CCH et al. J of Clinical Endocrinology & Metabolism 2021; 106(11): 3354-3366; Rickels MR & Elahi D. J of Clinical Endocrinology & Metabolism 2012; 97(11): 3915-3916.

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