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BLUE CROSS

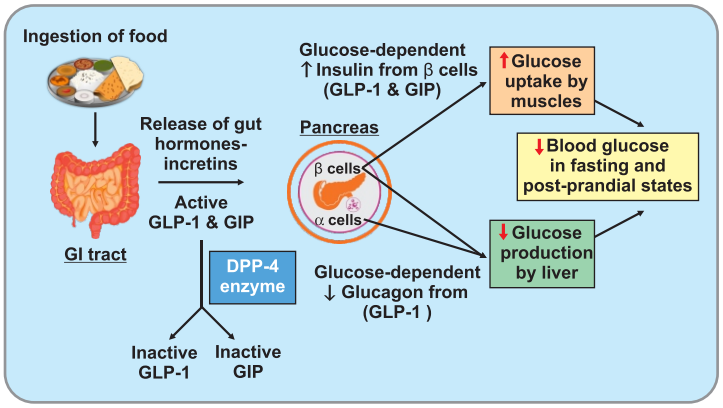
Medical Bulletin

Blue Cross Division

Gliptins: A new class of OADs

Incretins

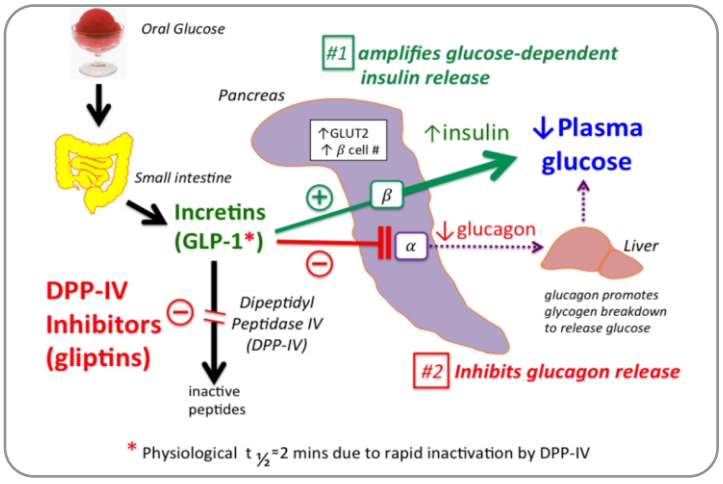
Incretins are gut hormones secreted from enteroendocrine cells into the blood within minutes after eating. One of their many physiological roles is to regulate the amount of insulin that is secreted after eating. There are two incretins, known as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1),& both these incretins are rapidly deactivated by an enzyme called dipeptidyl peptidase 4 (DPP-4).



Role of Incretin Hormones on Blood Glucose

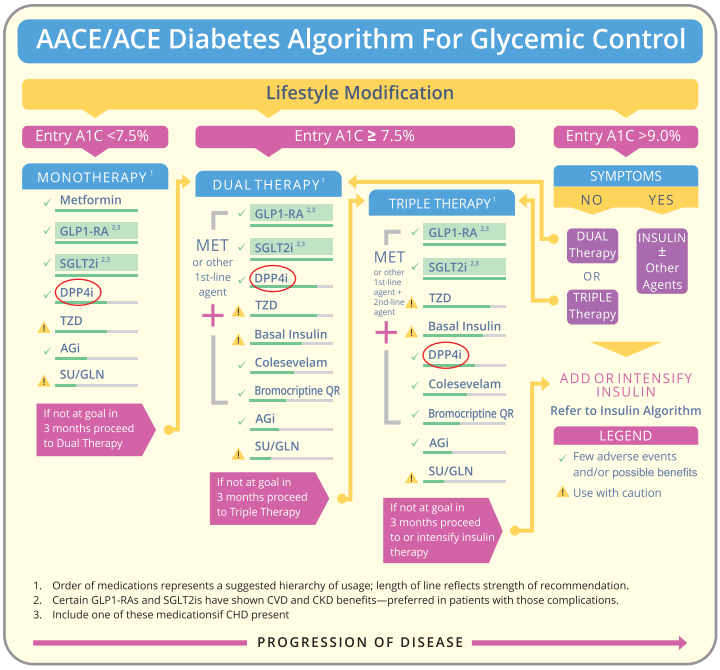
Dipeptidyl Peptidase-4 Inhibitors (Gliptins) Dipeptidyl peptidase 4 (DPP-4) inhibitors ('gliptins') block the DPP-4 enzyme mediated metabolism of incretin hormones, including glucagon-like peptide-1 (GLP-1) & glucose-dependent insulinotropic polypeptide (GIP), which are secreted by the intestine in response to food. This increases the levels of active incretins, prolonging their effect in stimulating insulin release and decreasing glucagon secretion.

Although various DPP-4 inhibitors have different PK & PD profiles, **they are similar with a very safe adverse effect profile (weight neutral without causing hypoglycemia).**



Current Position of Gliptins in Diabetes Management Guidelines

The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), European Society, and NICE (UK) guidelines suggest that gliptins should be considered over other anti-diabetic therapies, especially if the patient is experiencing an increased incidence of hypoglycaemia and overweight.



As "Add On Therapy to Metformin"

Clinical data suggests that when a gliptin is added onto patients inadequately controlled with metformin there results a substantial improvement in HbA1c with as many twice as number of patients achieving an HbA1c of <7% compared to metformin alone.

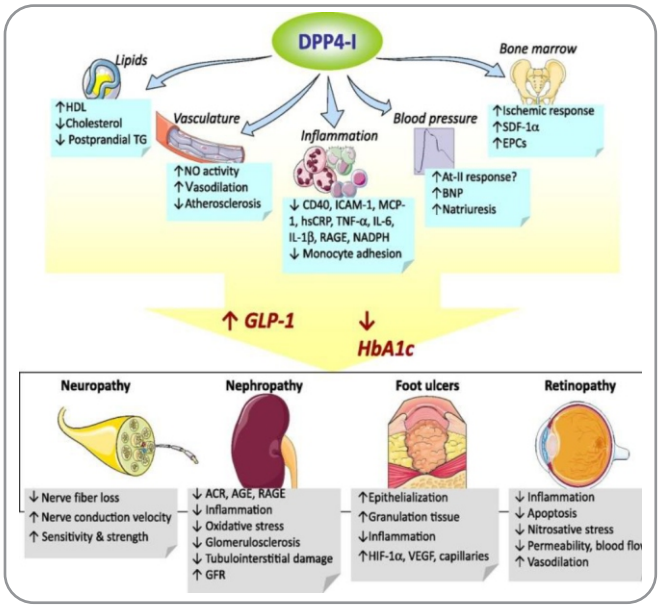
Furthermore, for the first time data has suggested that in patients with HbA1c between 7% and 8% while on metformin therapy rather than optimizing the dose of metformin from 1 to 2 gms/day or greater (as most existing guidelines suggest), by adding a gliptin to an already existing dose of metformin the degree of HbA1c reduction is greater than that achieved by up-titrating the dose of metformin, with far greater number of patients achieving HbA1c target of <7%.

Current Indications for Use of Gliptins

- First line in T2DM with HbA1c <7%.
- Second line as add-on therapy in T2DM patients already on one out of the following (metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, miglitinide) for uncontrolled T2DM.
- Third line as add-on therapy in T2DM patient's already on combination therapy (2 out of the following metformin, SU, TZD, AGIs, miglitinide).

Future Prospects

- Currently, gliptin therapy is restricted to glycaemic control in T2DM patients. However, DPP4 inhibitors seem to represent a promising therapeutic approach for the treatment of vascular diseases in addition to glucose control. *In vitro* and preclinical models have shown beneficial effects on vascular function, endothelial regeneration, and inhibition of atherosclerosis via various signalling pathways. Furthermore, DPP4 inhibitors are a well-tolerated class of drugs in diabetic and non-diabetic patients after acute coronary syndrome.



A schematic representation summarizing the roles of DPP-4 inhibition.

Summary

Gliptins have revolutionized the concept of diabetes management & have provided an effective and safe option in its armamentarium.

Gliptin: Is there any cost effective option available?

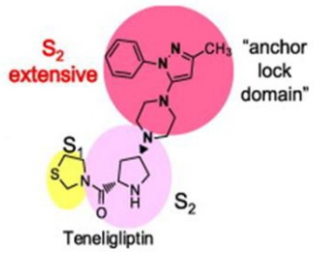
YES- Teneligliptin

Teneligliptin is the most cost effective amongst all the gliptins available in India currently.

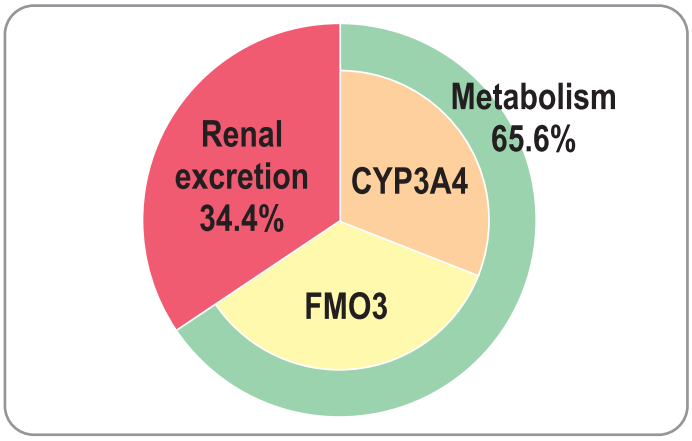
-Teneligliptin, a 3rd generation gliptin offers unique pharmacodynamic advantage with unique ''**J shaped anchor– lock domain''** , which provides potent and longer duration of action.

-Teneligliptin offers pleotropic benefits such as improvement in endothelial function, left ventricular function, and lipid levels.

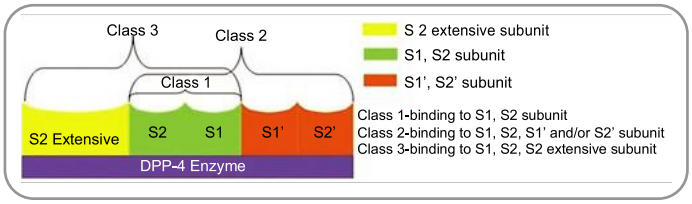
-Teneligliptin serves as an appropriate add-on to metformin early in therapy to delay exhaustion of pancreatic islet function.



- Teneligliptin has dual mode of elimination via renal and hepatic, and hence **can be administered safely in renal impairment patients.** Also, dosage adjustment is not required in patients with mild to moderate hepatic impairment.



Comparative studies have determined binding modes of DPP-4 inhibitors with the active site of DPP-4 enzyme. **The DPP-4 enzyme has five binding sites (sub-sites), namely, S1, S2, S1', S2', and S2 extensive.**



Classification of Gliptins based on Selectivity for DPP-4 enzyme

Teneligliptin is a class 3 DPP-4 inhibitor; it binds to additional site of S2 extensive and produces more extensive DPP-4 inhibition. The binding to this site is tighter than the binding to the other sub sites, and hence provides a more effective and longer duration of DPP-4 inhibition.

References

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- *Remm F, et al. European Heart Journal - Cardiovascular Pharmacotherapy 2016; 2(3): 185-193.*
- *Sharma S K, et al. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2016; 9: 251–260.*
- *Maladkar M, et al. Journal of Diabetes Mellitus 2016; 6: 113-131.*

Infantile Colic

What is colic and who gets it?

While colic is often associated with infants, it can occur in adults, too. In babies, colic is usually described as uncontrollable crying for several hours and weeks for no apparent reason.

In adults, colic is a pain, usually intestinal or urinary in nature, that comes and goes and that intensifies and then gradually eases. In adults, this colicky pain can be a one-time occurrence or recur weeks, months, or even years after the initial episode.

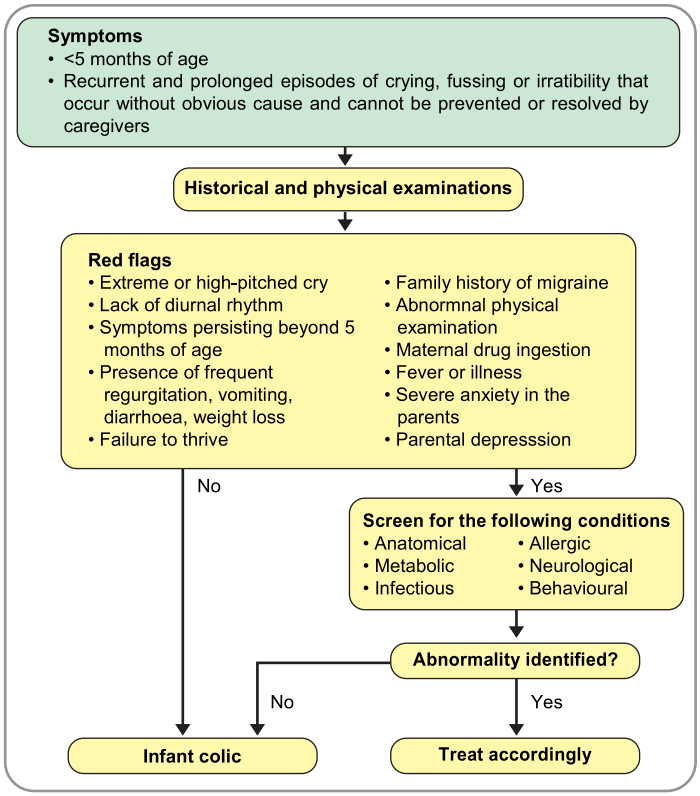
What is infantile colic?

Infants cry a lot. And that's completely normal. Babies generally cry to express a need or want and may cry because they are: tired, hungry, wet, overstimulated, and needing some attention.

Colicky crying differs from ordinary crying in that these otherwise healthy babies cry for no obvious reason and remain inconsolable for hours.

Colic in infant means crying for more than three hours a day, three plus days a week, for three plus weeks. The crying often begins in the evening.

Infant colic is often accompanied by flushing of the face, a frown, tensing of the abdomen, clenching of the fists and drawing up of the legs. Important additional clinical features of infant colic are its prolonged, hard-to-soothe and unexplained nature.



Diagnostic Algorithm for Infant Colic

What is incidence of colic?

Global prevalence of infantile colic is estimated to be around 20% (one out of five babies suffers from colic). Colic is fairly common in India, affecting from 10 to 40% of infants. **Twice as many infants have colic if their mother smoked during pregnancy.**

What causes colic in babies?

The pathogenesis of infant colic remains unclear and is thought to be multifactorial.

Pathophysiology of infant colic is broadly classified as non-gastrointestinal or gastrointestinal origin.

The non-gastrointestinal causes of colic include:

- Behavioral causes,
- Altered parent-child interaction,
- Immaturity of CNS, and
- Early form of migraine.

The gastrointestinal causes of colic include:

- Lactose intolerance (lactase deficiency in early infancy leads to lactose malabsorption and increased gas production which in turn acts as a source of discomfort for infants),
- Altered gut flora (decrease in commensal bacteria like *Lactobacillus* and *Bifidobacter* in gut of babies),
- Immaturity of enteric nervous system,
- Increased motilin receptors,
- Cow milk hypersensitivity.

Also, colic may be associated with intestinal discomfort stemming from:

- A food allergy or sensitivity.
- Over or underfeeding.
- Infrequent burping.
- Improper digestion.

Does breast feeding/bottle feeding causes colic?

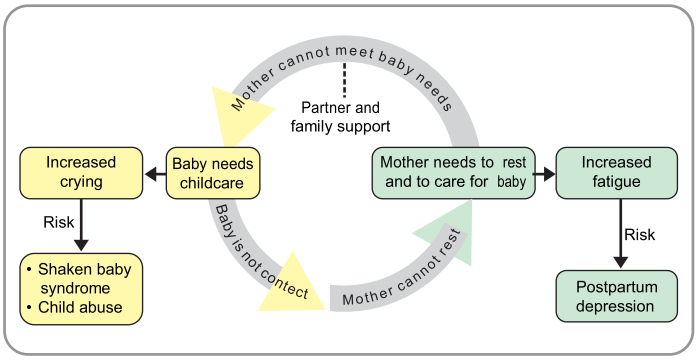
It has been shown that the early mode of enteral nutrition does not affect the incidence of colic i.e., whether the child is breast fed or bottle fed does not affect the incidence of colic.

During breastfeeding, a baby can swallow lot of air. Air trapped in the stomach and intestines can cause gas and stomach pain. Breastfed babies tend to take in less air during feedings than bottle-fed babies.

Breastfeeding is not a cause of colic, and babies who take infant formula/bottle-feed get colic, too. Similar prevalence, amount and pattern of crying are reported

between infants fed with human milk, formula or formula supplemented milk. **Contrary to this, one study reported a higher prevalence of colic symptoms in formulafed infants than in breastfed infants.**

Also, **dietary changes during lactation** like consumption of milk products, caffeine, and foods like onions and cabbage can distress baby's sensitive stomach.



Risk Associated with Infant Colic/Crying on Mother's Health

When to see a doctor?

Persistent crying could be colic, which isn't considered harmful to the baby. But long periods of crying may also signal some kind of physical distress. If the baby is found to be otherwise healthy, they will be diagnosed with colic. Laboratory tests or scans are not usually necessary unless the doctor suspects there may be an underlying cause. Colic in infants can also cause distress on mother's health.

How is colic in babies treated?

Probiotic/*Lactobacillus reuteri:* If baby is on breastfeeding, five drops of the probiotic *Lactobacillus reuteri* can be given daily. In one study, adding this probiotic was seen to reduce crying in breastfed babies with colic by 61 minutes, although it increased crying in bottle-fed babies.

Simethicone: Simethicone is an anti-foaming agent that reduces the amount of trapped wind and thus, relieves abdominal pain. It brings together small bubbles of gas that are trapped in the stomach contents when the baby swallows air. As the bubbles group together and become larger, they are easier to expel by burping or passing wind. Simethicone works locally in the gut and does not get absorbed into the bloodstream.

Lactase drops: Lactase is an enzyme that breaks down milk sugar lactose into glucose and galactose. People with lactase deficiency in the gut can develop abdominal cramping and diarrhea after consuming milk products. Lactase helps to prevent this. Thus, lactase drops may be helpful in infants with colic.

Hydrolyzed infant formula/ infants with cow milk allergy (CMA): In infants shown to have CMA, dietary modification is recommended. In exclusively breast fed infants with CMA, breast feeding should be continued but all forms of milk products should be restricted from the mother's diet. In a mixed-fed infant with CMA, the baby should be given only breast feed and no restriction of maternal diet is required. In a formula fed infant with CMA, extensively hydrolysed formula should be considered.

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- *https://www.healthline.com/health/colicky-pain#treatment-in-adults.*
- *Sarasu J M, et al. Indian Pediatrics 2018; 55:979-987. https://www. indianpediatrics.net/nov2018/nov-979-987.htm.*
- *Zeevenhooven J, et al. Nature Reviews Gastroenterology & Hepatology 2018; 15: 479-496.*

Can Eye Drops Dissolve Cataracts?

The news has been buzzing with reports of a new eye drop that may one day allow for cataracts to be treated without surgery.

Chinese and American scientists and ophthalmologists have found that a natural chemical called as lanosterol may stop the development of cataracts, the leading cause of blindness worldwide.

Lanosterol is a naturally occurring steroid which keeps the human lens clear by stopping the breakdown and clumping of the normally clear proteins in the lens.

The researchers developed an eye drop solution made of lanosterol and tested the solution on dogs, rabbits and synthetic cataracts developed in labs using cells from human lenses. They found that the drops shrank cataracts significantly in all three groups.

Studies showed that when lanosterol was applied to the human lens cells, lens proteins stopped clumping and transparency increased.

Scientists are working hard to prove the benefits of using **lanosterol** as a non-invasive alternative to cataract surgery. ***Treating cataracts with eye drops instead of undergoing cataract surgery is certainly a possibility for the future.***

References:

- *https://www.verywellhealth.com/eye-drops-for-cataracts-3421711.*
- *https://www.aao.org/eye-health/news*

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