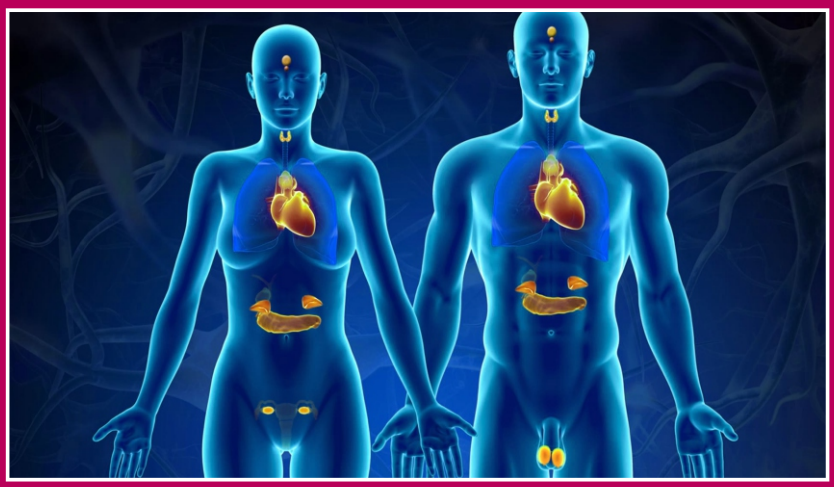
NEWS LINE

KARNATAKA ENDOCRINE SOCIETY

3rd Issue | December 2023

THEME - JOURNEY OF DIABETES MELLITUS MANAGEMENT



- Understanding Diabetes Reversal / Remission
- Place of Gliptin in the era of SGLT2 Inhibitors
- SGLT2 Inhibitors - Blockbuster molecule in Type 2 Diabetes
- Intermittent Fasting: Boon or Curse in the management of Diabetes?

PRESIDENT MESSAGE

Dear Colleagues,

It's a great honor for me to serve as the President, Karnataka Endocrine Society. I thank all the members of the Society for this opportunity, and we have done quite a significant academic job and most physicians, Pediatricians, Gynecologists and Obstetricians are aware of our work. We need to spread the awareness to other medical specialties in Karnataka. We are conducting monthly case discussions in virtual platform, three monthly physical meeting inviting people across specialties from India who have original works and most importantly the Annual conference, Hormone Rhythm. This Newsletter is our third Edition on various issues on Diabetes in our clinical practice keeping in my mind our colleague physicians. This is in follow up with our second newsletter published three months back which received a huge positive response from doctor colleagues across Karnataka of different specialities. I wish the very best to the Editorial team for their efforts and all their present and future endeavors.

Warm regards,

Dr. Arpandev Bhattacharyya

EDITORIAL BOARD - MESSAGE

NAVIGATING DIABETES MELLITUS MANAGEMENT

Dear friends,

In recent years, a nutritional trend has gained significant traction, capturing the attention of health enthusiasts and researchers alike—Intermittent Fasting (IF) and Diabetes Reversal. This editorial aims to shed light on the science behind above.

Intermittent fasting is a compelling and evolving area of research in the realm of health and wellness. While it presents a potential tool for weight management and overall well-being, it is not a one-size-fits-all solution. As we continue to unravel the science behind intermittent fasting, responsible and informed adoption of this eating pattern, guided by professional advice, may offer a pathway to improved health and vitality. While intermittent fasting shows promise, it is essential to approach it with caution. Not everyone may benefit from this eating pattern, and individual responses can vary. It is crucial to consult with healthcare professionals

In the global fight against diabetes, a groundbreaking concept has emerged that challenges traditional notions of irreversible chronic conditions—Diabetes Reversal. Diabetes, has long been considered a chronic, lifelong condition requiring continuous management. However, recent research and success stories are challenging this paradigm, suggesting that for some individuals, diabetes may not be an irreversible sentence. The idea of diabetes reversal centers around adopting lifestyle changes that address the root causes of the disease.

Warm regards,

Dr. Vageesh Ayyar Subramanyam, Dr. Chitra Selvan
Editorial Board

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UNDERSTANDING DIABETES REVERSAL / REMISSION

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In the evolving landscape of Type 2 Diabetes Mellitus (T2DM) management, the concepts of diabetes reversal and remission are gaining significant attention. To clarify these concepts and their implications, we present a question-and-answer themed article, providing insights for both healthcare professionals and patients.

Q1) What is the current understanding of diabetes reversal in T2DM?

Diabetes reversal in T2DM refers to a state where blood glucose levels return to normal or near-normal levels without diabetes medication. This is primarily achieved through lifestyle interventions, including significant weight loss and dietary changes. However, it's important to understand that this does not constitute a permanent cure. The risk of relapse remains if lifestyle changes are not sustained.

Q2) How is diabetes remission defined clinically?

Clinically, diabetes remission in T2DM means achieving a glycated hemoglobin (HbA1c) level below 6.5% without the use of glucose-lowering medication for at least 3 months. This definition, set by WHO and ADA, helps standardize criteria for remission in research and clinical practice.

Q3) What is the difference between diabetes reversal and diabetes remission?

While often used interchangeably, these terms have distinct meanings. Diabetes reversal implies normalizing blood glucose levels through lifestyle changes, without suggesting a permanent cure. Diabetes remission, a more clinically accepted term, refers to minimizing the disease's effects by maintaining normal blood glucose levels without medication, acknowledging the ongoing risk of relapse.

Q4) Which term is more accurate: diabetes reversal or diabetes remission?

"Diabetes remission" is generally regarded as more accurate and clinically appropriate. It acknowledges the chronic nature of T2DM and the ongoing nature of its management.

Q5) What are the pros and cons of the commercialization of diabetes reversal in India?

The commercialization has both benefits and drawbacks. It increases awareness and offers innovative treatment options, emphasizing preventive care. However, it also brings risks like misleading promises, quality and safety concerns, and potential financial exploitation of patients.

Q6) Is there evidence that beta cells in the pancreas can recover in diabetes reversal?

Yes, studies suggest that under certain conditions, beta cells can normalize their function and volume, which is crucial for diabetes reversal. This can occur through various interventions, including dietary changes and bariatric surgery.

Q7) Which patients are best suited for diabetes reversal?

Ideal candidates are those early in their diagnosis, with mild to moderate disease severity, primarily linked to obesity, capable of significant weight loss, motivated for lifestyle changes, with good beta-cell function, without severe complications, and with adequate support systems.

Q8) How does the approach to diabetes reversal differ for newly diagnosed versus long-term patients?

The approach to diabetes reversal can vary significantly between newly diagnosed patients and those who have been managing T2DM for a longer period.

For Newly Diagnosed Patients:

Early Intervention: Reversal strategies are more effective when implemented soon after diagnosis. This is due to better preservation of pancreatic beta-cell function.

Lifestyle Changes: Emphasis is placed on immediate lifestyle interventions, including diet and exercise, which can be highly effective at this stage.

For Long-term Patients:

Assessment of Beta-Cell Function: For patients with long-standing T2DM, it's important to assess the remaining beta-cell function, as this influences the likelihood of successful reversal.

Integrated Approach: Treatment may involve a more integrated approach, combining lifestyle changes with medication adjustments.

Management of Complications: Long-term patients might have developed complications, which need to be managed alongside reversal efforts.

Behavioral Support: Given the challenges of changing long-established habits, more intensive behavioral support and counseling might be necessary.

PLACE OF GLIPTIN IN THE ERA OF SGLT2 INHIBITORS

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Introduction:

Recent years have seen noteworthy shifts in diabetes treatment, moving beyond glycemic control to a holistic approach addressing risk factors. The novel drug classes, such as sodium-glucose transporter 2 inhibitors (SGLT2-i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA), have demonstrated additional cardiovascular and renal benefits apart from their glucose-lowering effects. These findings consequently changed the guidelines for the management of hyperglycemia in patients with type 2 diabetes mellitus. This shift prompts a reevaluation of previously utilized agents, such as dipeptidyl peptidase 4 (DPP-4) inhibitors commonly known as gliptins.

Incretin history and evolution of gliptins:

DPP-4 inhibition is a promising therapy for Type 2 Diabetes Mellitus (T2DM), centered on enhancing the incretin effect. In 2006, sitagliptin, the first DPP-4 inhibitor, received approval for diabetes treatment.

The incretin effect refers to the increased insulin secretion in response to oral glucose intake. The first reported incretin, glucose-dependent insulinotropic peptide also known as Gastric Inhibitory Polypeptide (GIP), is secreted by K-cells in the duodenum and jejunum upon consumption of carbohydrates or lipids. The second vital incretin hormone, GLP-1, originates from L-cells in the distal ileum and colon. In normal individuals, GLP-1 serves various physiological roles, such as glucose-dependent insulin secretion, prevention of inappropriate glucagon secretion from the pancreas, and slowing of gastric emptying. In type 2 diabetes, there is a decrease in GLP-1 secretion, contributing to the impaired "incretin effect." Nonetheless, the rapid degradation of both GLP-1 and GIP by the DPP-4 enzyme renders them ineffective, leading to their extremely brief half-life of less than 2 minutes.

There are two key strategies in designing drugs for T2DM that leverage the incretin effect. The first involves GLP-1RA, which share similarities in their sequences with native GLP-1 enabling them to bind and stimulate the GLP-1 receptor while remaining resistant to DPP-4 degradation. The second approach focuses on inhibiting the DPP-4 enzyme by DPP-4 inhibitors to prevent the degradation and inactivation of GLP-1 and GIP. These inhibitors typically reduce serum DPP-4 activity by over 80%, resulting in doubled active GLP-1 concentration, significant postprandial glucose level reduction, and an approximately 0.8% decrease in HbA1c. Crucially, DPP-4 inhibitors pose no heightened risk of hypoglycemia because of glucose-dependent insulin secretion from pancreatic β-cells by the GLP-1.

Available gliptins:

The various gliptins available as oral formulations include Sitaglitin, Vildagliptin, Linagliptin, Saxagliptin and Alogliptin. Variations in their chemical structure impact their pharmacokinetic properties, formulation, and daily dosing (Table 1A). Sitagliptin, linagliptin, and alogliptin, with their extended half-lives, allow for once-daily dosing. Saxagliptin, despite its short half-life, can be administered once daily due to the presence of its active metabolite, BMS-510849. Vildagliptin, with a short half-life, requires twice-daily dosing. In chronic kidney disease (CKD), all DPP-4 inhibitors can be used across all stages with reduced doses, whereas linagliptin does not require dose adjustment. (Table 1B).

Safety profile:

The safety profile of gliptins is generally favorable and are well-tolerated by most patients. Gliptins are known for their neutral effect on body weight and a low risk of hypoglycemia, making them attractive options for patients who need to avoid weight gain or are at risk of low blood glucose.

In extensive randomized placebo-controlled trials, DPP-4 inhibitors demonstrated cardiovascular and overall safety in managing high-risk patients with type 2 diabetes. However, there is no evidence of their superiority in cardiovascular outcomes compared to controls. The elevated rate of hospitalizations for heart failure associated with saxagliptin in the SAVOR-TIMI 53 trial contrasts with the findings for other DDP-4 inhibitors in cardiovascular outcome trials (CVOTs), except for a non-significant increase in the EXAMINE trial with alogliptin. Consequently, regulatory authorities have issued warnings about the heightened risk of heart failure for saxagliptin and alogliptin, based on these observations.

Until a few years ago, acute pancreatitis and pancreatic cancer were considered significant safety concerns based on various reports and signals from clinical studies involving these drugs. However, a recent meta-analysis of randomized controlled trials found no substantial evidence supporting an association between DPP-4 inhibitors and pancreatitis or pancreatic cancer. However, the evidence concerning pancreatic cancer is limited, preventing definitive conclusions.

Additionally, these agents have demonstrated a low potential for drug interactions, contributing to their suitability for combination therapy with other antidiabetic medications.

Gliptins in special situations

While gliptins are generally well-tolerated and effective, their use in special populations requires careful consideration. One special population that often requires unique attention is the elderly. Gliptins may be preferable in older adults due to their favorable safety profile and lower risk of hypoglycemia compared to some other glucose lowering drugs. Additionally, gliptins are renally excreted, so dose adjustments may be necessary in patients with renal impairment, a common concern in the elderly. Patients with hepatic impairment may also require special attention when prescribing gliptins. While these drugs are primarily metabolized in the liver, they generally do not require dose adjustments in patients with mild to moderate hepatic impairment. However, caution is warranted in severe hepatic impairment, and alternative treatments may be considered. Regular monitoring and communication between healthcare providers and patients are essential to ensure the safety and efficacy of gliptin therapy in these special populations.

Practice pearls

Overall, DPP-4 inhibitors significantly lower blood glucose levels without a high risk of hypoglycemia and with a neutral impact on body weight. Their safety profile is generally favorable. Additionally, they are user-friendly, requiring no dose titration, and can be taken at any time of the day irrespective of meals.

Until recently, DPP-4 inhibitors were the primary choice post-metformin initiation. However, their position in the hyperglycemia management algorithm has shifted downward in response to the substantial findings from large-scale cardiovascular outcome trials (CVOTs) for newer glucose-lowering drugs such as SGLT2 inhibitors and GLP-1RA, which demonstrated significant benefits in morbidity and mortality.

However, DPP-4 inhibitors still have a prominent role in the treatment of the patients with T2DM particularly : 1) those with longstanding T2DM with co-morbidities requiring multiple glucose- lowering drugs, 2) Patients with renal impairment, where other glucose lowering medications might be contraindicated, 3) Frail elderly due to low risk of hypoglycemia, 4) In patients with ASCVD, heart failure, CKD as a third line therapy(after Metformin and SGLT2 inhibitors /GLP1RA) if therapeutic goals are not achieved.

In summary, DPP-4 inhibitors are a well-established and safe class of oral glucose-lowering agents that play a valuable role in diabetes management.

Table 1A: Characteristics of DPP-4 inhibitors

Drug	Dosage with normal renal function	Metabolism	Excretion	Half life (hours)	HbA1c reduction(%)	Dose modification in hepatic dysfunction
Sitagliptin	100mg once daily	Minimal	Predominatly renal	8-24	0.5-1.0	No
Saxagliptin	5mg once daily	Hepatically metabolized to active metabolite (via P450 3A4/5)	Metabolism (parent) Renal (parent + metabolite)	2-4 (parent) 3-7(metabolite)	0.5-1.0	No
Vildagliptin	50mg twice daily	Hydrolysed to inactive metabolite (P450 enzyme independent)	Metabolism (parent) Renal (parent + metabolite)	1.5-4.5	0.9 (mean value)	Not recommended in severe liver dysfunction
Linagliptin	5mg once daily	Minimal	Predominatly biliary (<6% renal)	10-40	0.5-0.7	No
Alogliptin	25mg once daily	Minimal	Predominanlty renal	12-21	0.6(mean value)	No

Table 1B: Dose modification of DPP-4 inhibitors in renal impairment

Drug	Dosage with normal renal function	Mild renal impairment (CrCl≥50ml/min)	Moderate renal impairment (CrCl≥30-50ml/min)	Severe renal impairment / ESRD (CrCl<30ml/min)
Sitagliptin	100mg once daily	Yes	Yes with dose adjustment (50mg once a day)	Yes with dose adjustment (25mg once a day)
Saxaglitin	5mg once daily	Yes	Yes with dose adjustment (2.5mg once a day)	Yes with dose adjustment (2.5mg once a day)
Vildagliptin	50mg twice daily	Yes	Yes with dose adjustment (50mg once a day)	Yes with dose adjustment (50mg once a day)
Linaglipitin	5mg once daily	Yes	Yes	Yes
Alogliptin	25mg once daily	Yes	Yes with dose adjustment (12.5 mg once a day)	Yes with dose adjustment (6.25 mg once a day)

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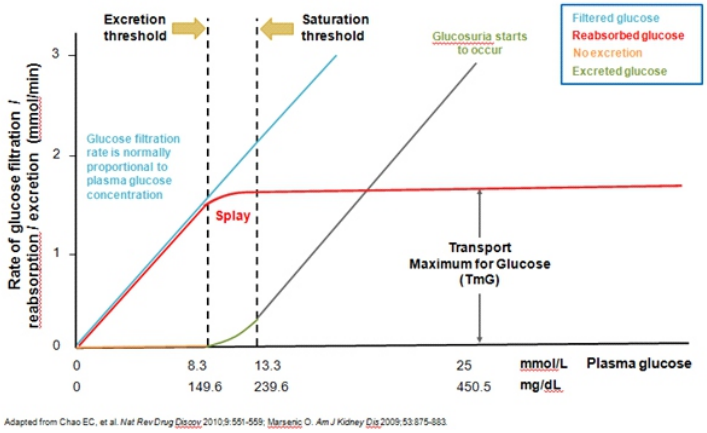
SGLT2 INHIBITORS - BLOCKBUSTER MOLECULE IN TYPE 2 DIABETES

Discovery of SGLT2 Inhibitors (Gliflozins)

The SGLTs belong to family of membrane proteins which transport glucose, vitamins, amino acids, osmolytes and ions across the luminal membrane of proximal convoluted tubule and the intestinal epithelium. In healthy humans about 150 grams of blood glucose is filtered through the glomerular membrane to the tubular lumen, most of which gets reabsorbed .The reabsorption of glucose is a two-stage process, SGLT2 and SGLT1 are responsible for the active transport of glucose and sodium across the apical membrane while GLUT2 passively transports the glucose to the plasma across basolateral membrane. Basolateral Na+/K+ pump facilitates the process by maintaining Na+ gradient across the apical membrane. In Diabetes the SGLT2 activity is up regulated. SGLT2 inhibitors inhibit their activity and by causing glycosuria helps in reducing blood glucose levels in Diabetes Mellitus.

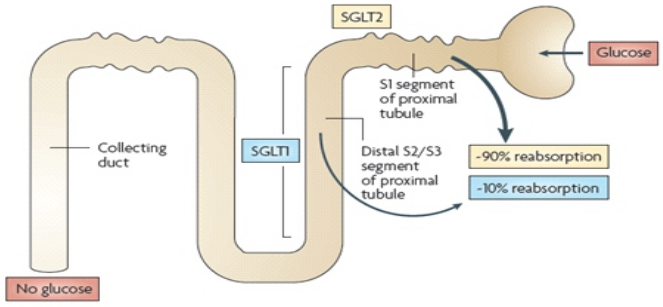
Phlorizin, a naturally occurring O-glycoside found in the root bark, leaves, shoots and fruit of the apple tree, was the first SGLT2 inhibitor to be discovered. It was first isolated by French chemists in 1835. Rossetti and his team compared the effects of phlorizin on blockade of renal glucose reabsorption in diabetic rats [partial pancreatectomy induced] with controls. Using euglycaemic hyperinsulinaemic clamp studies, phlorizin was found to normalize insulin sensitivity in these diabetic rats, but did not influence insulin action in controls. Phlorzin is easily metabolized in the intestinal tract by β-glucosidase and is also a nonselective SGLT inhibitor. The first orally available Phlorizin derivative reported was T-1095 but it too was non selective. Subsequent efforts to overcome these limitations led to the identification of the novel C-glucoside- containing selective SGLT2 inhibitor Dapagliflozin. SGLT2 inhibitors such as Canagliflozin, Empagliflozin and Ertugliflozin are based on the same meta C-glycosylated diaryl-methane pharmacophore.



Adapted from Chao EC, et al. *Nat Rev Drug Discov* 2010;9:551-559; Marsenic O. *Am J Kidney Dis* 2009;53:875-883.

Mechanism of action

SGLT2 inhibitors inhibit SGLT2 co-transporter mediated glucose reabsorption in Proximal renal tubule and causes glycosuria resulting in reduction in blood glucose without stimulating insulin release.



Comparision of available SGLT2 Inhibitors

Drug (dose)	Half-life (hours)	Oral bioavaila-bility (%)	Metabolism and elimination	SGLT2 selectivity (vs SGLT1)
Canagliflozin (100–300 mg OD)	10.6–13.1	65	Hepatic conjugated Renal excretion	~250 fold
Dapagliflozin (5–10 mg OD)	12.9	78	Hepatic conjugated Renal excretion	~1200 fold
Empagliflozin (10–25 mg OD)	12.4	60	Hepatic conjugated Renal excretion	~2500 fold
Ertugliflozin (5–15 mg OD)	16.6	100	Hepatic conjugated Renal excretion	~2000 fold
Remogliflozin (100mg BD)	1.4	93	Hepatic conjugated Renal excretion	~365 fold

Safety profile of Gliflozins

The safety profile of Gliflozins is generally good, when used alone there is no increased risk of hypoglycaemia and this is due to insulin independent mechanism of action. However they can increase the risk if used with other glucose-lowering agents like sulfonylureas or insulin. Gliflozins are associated with increased risk of genital infection though increased risk of UTI is not found to be high. SGLT2i are rarely associated with increased risk of Fourniers gangerene [necrotising fasciitis of perineal soft tissue]. Diabetic ketoacidosis (DKA) is a rare but serious adverse effect associated with the use of Gliflozins. Gliflozins may induce DKA by reducing insulin secretion and increasing glucagon secretion due to glycosuria, with consequent increased synthesis of free fatty acids that are converted to ketone bodies. Another adverse effect observed with this drug class is hypotension, which is related to volume depletion. Whether SGTL2 inhibitors increase the risk of amputation of lower limbs is still debated in clinical trials showing controversial results. In the CANVAS clinical trial program, Canagliflozin had a higher risk of amputation than placebo. However, there was no increased risk of amputation in CREDENCE trial. Although evidence on the risk of amputation are controversial, product's information have been updated to include a warning on this potential risk. Canagliflozin was also associated with the risk of bone fracture during the CANVAS program. However, this risk was not observed in other trials with Canagliflozin or other Gliflozins. Gliflozins They can cause an initial decline in the estimated glomerular filtration rate (eGFR), usually within the first months of treatment, due to intravascular volume changes this initial eGFR decline is usually small and not clinically significant. In the long-runthey reduce the decline of eGFR and protect kidneys.

Gliflozins beyond Diabetes control – Cardio-Renal-Metabolic (CRM) Continuum

Apart from Glycemic control Gliflozins have numerous extraglycaemic benefits due to its unique mechanism of action and pleiotropic effects. In a meta-analysis of studies comparing SGLT2 inhibitors with placebo, SGLT2 inhibitors have shown to reduce the risk of kidney disease progression

(defined as a sustained eGFR decrease (≥50%) from randomisation, end-stage kidney disease or death from renal failure) by 37% overall. Risk reduction was similar risk in patients with diabetes and without diabetes. In the four chronic kidney disease trials (CREDENCE, SCORED, DAPA-CKD, EMPA-KIDNEY) the relative risk for kidney disease progression were similar when analyses were separated by primary kidney diagnosis. In all four trials including patients with diabetic kidney disease, SGLT2 inhibitors reduced the risk of kidney disease progression by 40%. Data from patients with non-diabetic causes of chronic kidney disease were available from the DAPA-CKD and EMPA-KIDNEY trials. SGLT2 inhibitors reduced the risk of kidney disease progression by 30% in patients with ischaemic and hypertensive kidney disease, by 40% in patients with glomerular diseases. Compared with placebo, allocation to an SGLT2 inhibitors reduced the risk of acute kidney injury by 23% overall, with similar reductions observed in patients with diabetes and patients without diabetes.

In a metanalysis including 11 CVOT Trials, the risk of composite CV mortality or hospitalization for HF was reduced by 23% compared with placebo. In the subanalysis of participants divided according to the presence or absence of T2D there was no difference in the risk of the composite CV death or hospitalization for HF between the two groups. In the four trials that included participants with or without T2D (DAPA-HF, DAPA-CKD, EMPEROR-R and EMPEROR-P), treatment with Dapagliflozin (DAPA) or Empagliflozin (EMPEROR) was associated with 26% and 23% lower risk of the composite CV death or hospitalization for HF in patients with or without T2D, respectively. In the overall analysis including all the 11 CVOTs, the risk of CV mortality was reduced by 16% by treatment with SGLT-2 inhibitors, with moderate and significant heterogeneity. In the analysis of 6 CVOTs (EMPA-REG, CANVAS, DECLARE, CREDENE, VERTIS-CV, SCORED) the risk of MACE was reduced by 12%, with low heterogeneity. There was no difference in the risk of MACE according to the presence or absence of established CV disease at baseline.

To date, the most meaningful class effect of SGLT-2 inhibitors appears to be that on HF hospitalization for the following reasons as the reduced risk for HF hospitalization is > 25% in every CVOT published until now. So, we can be confident that the beneficial effect of SGLT-2 inhibitors to reduce the risk of hospitalization for HF is a class effect and is independent of the diabetes status, heart status (presence or absence of HF or established CV disease at baseline) and kidney status

Gliflozin and vascular Euphoria: EUPHORIA an acronym describes various vascular effects of Gliflozins.

E(Endothelial Function Improvement) Gliflozin causes in recovery of reactivity of blood vessels, and endothelial cells by reducing inflammation and oxidative stress in T2DM .

U(Utilization of Energy-substrates) Gliflozins affect cellular energetics and metabolism, glycosuria results in calorie-restriction mimicry causing substrate switch with increased utilization of adipose tissue for energy requirements resulting in weight-loss and improved insulin sensitivity, At the cellular level, this may result in stimulation of the key energy regulator, adenosine monophosphate activated protein kinase (AMPK), as well as sirtrulin-1 (SIRT1) which is implicated in improved cellular energetics .Inhibition of sodium-hydrogen exchanger (NHE-1) improves mitochondrial calcium levels improving mitochondrial metabolism and ATP-generation, even in response to ischemic myocardial stress.

P (Pressure and Volume Off-loading) Gliflozins causes natriuresis and glycosuria mediated osmotic diuresis resulting in reduced volume overload which may improve heart failure outcomes .SGLT2- inhibition exerts more prominent interstitial fluid-volume reduction, than intravascular volume which may limit the reflex neurohumoral stimulation seen in diuretics. In kidney, Natriuresis and resultant activation of tubuloglomerular feedback results in vasoconstriction of afferent arterioles causing fall in glomerular pressure and hyperfiltration which protects the nephrons in long-term.

H (Hemoconcentration) Increased oxygen requirement in renal medulla, secondary to increased sodium reabsorption, is postulated to stimulate erythropoiesis resulting to modest increase in haematocrit.

O (Oxidative Stress Reduction) Gliflozins reduce oxidative stress through reduced free radical generation and increased scavenging of free radicals. Reduction of hyperglycemia and uric acid levels also reduce oxidative stress. The net effect is a reduction in vascular damage, and improvement in vascular stiffness.

R (Reverse LV remodelling) Gliflozins cause regression of left-ventricular mass index and possibly reverse pathological myocardial remodeling. They improve cardiac structure and function, in patients with cardiac diseases regardless of T2DM

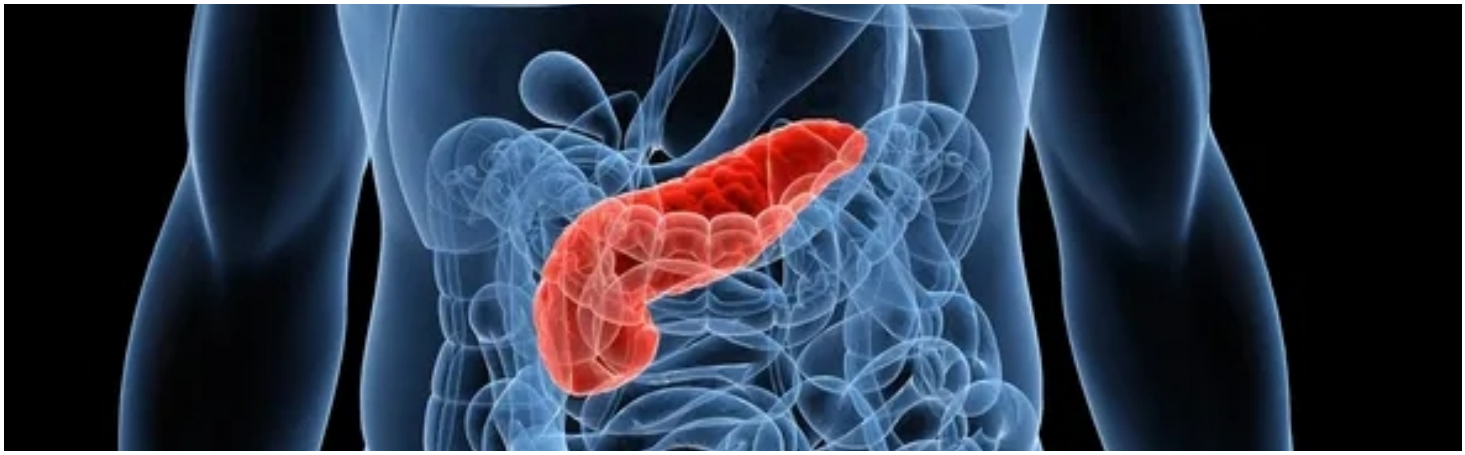
I (Inflammation Control) Gliflozins reduce chronic inflammation through substrate switch causing lowered activity of inflammatory adipokines and also by reduce NLRP3-inflammasome activation. This mechanism may have beneficial effect on atherosclerotic CV disease, as well as heart failure.

A (Autonomic Balance) Gliflozins also shown to improve autonomic balance, in patients with T2DM. Volume-depletion and hypotension mediated by these agents without increased sympathetic activity, and heart rate. Reduced renal cortical oxygen demand and consequently reduced renal afferent sympathetic activation, are plausible mechanisms of SGLT2-inhibitor related autonomic improvements

Practice pearls for clinicians

Gliflozins are one of the preferred OADs in diabetic patients with overt atherosclerotic cardiovascular disease (CVD), heart failure (with or without Diabetes), chronic kidney disease (to reduce the rate of decline in eGFR and albuminuria). Patients must be explained regarding the risk of genital fungal infection. Prior to starting an SGLT2 inhibitor, volume status and kidney function (serum creatinine with eGFR) should be assessed. Hypovolemia should be corrected prior to initiating an SGLT2 inhibitor. Diuretics and blood pressure medications may require dose adjustment prior to the use of SGLT2 inhibitors. To reduce the risk of hypoglycemia, patients using insulin or insulin secretagogues (Sulfonylureas, Glinides) may require a dose reduction with initiation of SGLT2 inhibitors. They should be used with caution in patients with risk factors for foot ulceration and avoided in patient with history of Diabetic ketoacidosis. Patients at risk for falls and fracture may benefit from assessment of bone density.

In Summary, day has come now that if we do not prescribe a patient with Type 2 Diabetes Mellitus Gliflozin, we will have justify why. This will also be true in cases of non-Diabetic kidney disease and heart failure.



INTERMITTENT FASTING: BOON OR CURSE IN THE MANAGEMENT OF DIABETES?

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Introduction

Intermittent fasting (IF) has become increasingly popular recently. A normal day of an individual consists of at least 3 meals with or without snacks. However , our ancestors spent more time in fetching food and hence did not have the luxury for the same. IF has been found useful in tackling obesity and diabetes. The concept of intermittent fasting is not new- it has been found throughout human civilization in various cultural and religious traditions in different forms. The renewed interest in different IF regimens is evident by the plethora of press publications, social media and diet recommendations.

Benefits of Intermittent fasting

The scientific evidence for IF is often extrapolated from animal studies. However ,there are human studies and meta-analyses which also demonstrate the benefit of intermittent fasting.

Preclinical studies and clinical trials have shown that intermittent fasting has broad-spectrum benefits for many health conditions, such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders. Animal models show that intermittent fasting improves health throughout the lifespan. However, most of the clinical studies are relatively short term interventions (months) and hence long term implications of intermittent fasting are still not known.

Type	Protocol	Commonly followed diets
Complete Alternate Day Fasting	Alternative fasting days (no energy containing food or beverages consumed) & eating days	
Modified Fasting Regimens	20-25 % of energy needs of scheduled fasting days.	5:2 diet (energy restriction 2 non-consecutive days and normal diet 5 days
Time restricted feeding	Allow individuals to consume ad libitum energy intake within specific time window	12:12 diet. where an individual consumes food in a 12 hours window. 8:16 diet where the individual consumes food in 8 hours window in a day
Religious fasting	A wide variety of fasting regimens are undertaken for religious and spiritual purposes	Ramadan (Muslim) - fasting from dawn to sunset for 29-30 consecutive days
		Yom- Kippur (Judaism) 1 day fasting for 24 hours
		Proşadhopavāsa (Jainism) fasting on Day 8 and Day 14 of the lunar cycle (rice, wheat, water , sweets and oral fresheners are restricted)
		Lent (Christianity) fasting for 40 days during the daytime (abstinence from meat, eggs, dairy products, olive oil and alcohol)
		Baguan zhai (Buddhism) : meal restriction after noon till next morning
		Ekadashi (Hinduism) fasting 11th day of lunar calendar

Religious fasting is practiced by people of most faiths, including Islam, Christianity, Hinduism, Buddhism, Jainism, Judaism, and Taoism. It is characterized by a variance in the degree of caloric restriction and abstinence from specific foods. Caloric intake is restricted to very early morning, evening, and nighttime. There is a dearth of prospective and randomized control trials in this field.

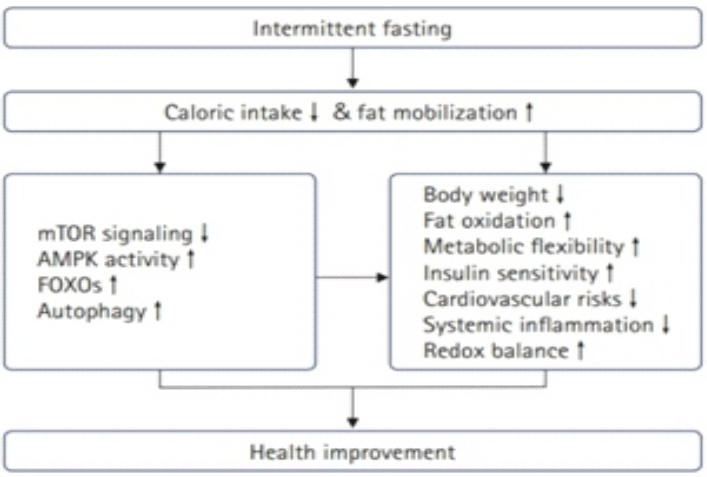
Physiology and Mechanism

According to Weindruch and Sohal in a 1997 article in the Journal, reducing food availability over a lifetime (caloric restriction) has remarkable effects on aging and the life span in animals.(1) During fasting, cells activate pathways that enhance intrinsic defenses against oxidative and metabolic stress and those that remove or repair damaged molecules

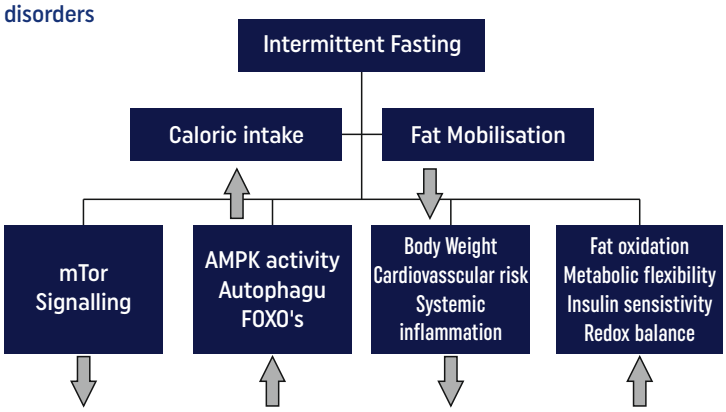
Physiology and metabolic switching

Glucose and fatty acids are the main sources of energy for cells . During periods of fasting, triglycerides are broken down to fatty acids and glycerol, which are used for energy. The liver converts fatty acids to ketone bodies, which provide a major source of energy for many tissues, especially the brain, during fasting .

Normally ketone bodies are low in humans, they rise within 8 to 12 hours after the onset of fasting, reaching levels as high as 2 to 5 mM by 24 hours. The metabolic switch from the use of glucose as a fuel source to the use of fatty acids and ketone bodies results in a reduced respiratory-exchange ratio (the ratio of carbon dioxide produced to oxygen consumed), indicating the greater metabolic flexibility and efficiency of energy production from fatty acids and ketone bodies . Ketone bodies are also potent signaling molecules with major effects on cell and organ functions . They have a role in regulating peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α), fibroblast growth factor 21,22,23 nicotinamide adenine dinucleotide (NAD+), sirtuins,24 poly(adenosine diphosphate [ADP]–ribose) polymerase 1 (PARP1), and ADP ribosyl cyclase (CD38). Ketone bodies also stimulate the expression of brain-derived neurotrophic factor , with implications for brain health and psychiatric and neurodegenerative



disorders



Effects of Intermittent fasting on health aging

Cells respond to intermittent fasting by increasing the expression of antioxidant defenses, DNA repair, mitochondrial biogenesis and autophagy. IF inhibits the mTOR protein synthesis pathway. The benefits of IG are beyond that conferred by weight loss. In a study where 16 healthy individuals were put on alternate day fast- they lost 2.5% of their initial weight and 4% of fat mass, with a 57% decrease in fasting insulin levels.

Physical and Cognitive Effects of intermittent fasting

Young men who fast daily for 16 hours lose fat while maintaining muscle mass during 2 months of resistance training Studies in animals show that intermittent fasting enhances cognition in multiple domains, including spatial memory, associative memory, and working memory.

Effect of Intermittent Fasting (IF) on glycemic control

Caloric restriction (CR) without producing malnutrition is the target in the treatment of obesity, type 2 diabetes and its associated metabolic risk factors. CR in obese subjects improves cardiovascular risk factors, insulin sensitivity, and mitochondrial function. But, in practice it is difficult to adhere to long-term daily CR. Hence, people resort to IF, which gives a little flexibility in eating on few days.

Mechanisms of CR-mediated improvement of glucose metabolism are not fully elucidated, but possibly involve significant alterations in insulin sensitivity of skeletal muscle, along with the reduction of fat mass. Fasting induced increase in circulating adiponectin is at least partly responsible for improvement in insulin sensitivity. Intermittent fasting increases insulin sensitivity on the whole body level as well as in adipose tissue support the view that cycles of feast and famine are important as an initiator of thrifty genes leading to improvements in metabolic function

Medically supervised, therapeutic fasting regimens can help reverse type 2 diabetes (T2D) and minimize the use of pharmacological and possibly surgical interventions in patients with T2D and obesity. Therapeutic fasting is an underutilized dietary intervention that can provide superior blood glucose reduction compared with standard pharmacological agents.According to Arnason TG et al, short term daily IF may be a safe, tolerable, dietary intervention in T2DM patients that may improve key outcomes including body weight, fasting glucose and postprandial variability. IF significantly improves glycemic control and insulin resistance with a reduction in BMI, a decrease in leptin level, and an increase in adiponectin concentration in the general population without chronic metabolic disease. Intermittent fasting was more beneficial in reducing body weight, waist circumference, and fat mass without affecting lean mass compared to the non-intervention diet. IF also effectively improved insulin resistance and blood lipid conditions compared with non-intervention diets. However, IF showed less benefit over continuous calorie restriction

Hypoglycemia
Hyperglycemia
Diabetic ketoacidosis
Dehydration and thrombosis

Modification of anti diabetic medications during IF

1. DPP IV inhibitors, Metformin: No modification needed
2. SGLT2 inhibitors: To be used with caution, if fluids are also restricted
3. GLP1 analogs: Can be used unless there is severe nausea/vomiting
4. Insulin
   - Long-acting basal insulin: Adjustments might not be required [Upto 10 IU reduction, if they are taking > 30 IU/day]
   - Short-acting analogues: To be withheld on fasting days [to be taken before meals and anticipated carbohydrate intake]
   - Premixed insulins (i.e, intermediate-acting and short-acting insulin): Not recommended during IF [as they are not adaptable to changes in meal timing and calories]
   - Any insulin use: Reduction by up to 70% on fasting days*
5. Sulfonylureas
   - Glibenclamide: Better avoided
   - Long acting SU (Glimepiride/extended release Gliclazide/Glipizide): Dose to be reduced to half; preferably to be taken before meals
   - Short acting SU (Gliclazide/Glipizide): Dosage frequency to be reduced; only to be taken before meals

Modification of anti diabetic medications during IF based on HbA1c

- < 7%: Pretrial discontinuation of all insulin and SUs
- 7-10%: Discontinuation of insulin only on fast days
- > 10%: No change in medication

Therapeutic considerations and lifestyle modifications:

During the fasting period, the individual with diabetes is predisposed to hypoglycaemia. "Defensive liquid snacking" during non fasting periods can lead to hyperglycaemia and related complications. Also intake of heavier meals can contribute to hyperglycaemia and weight gain.

Patients should be explained about the need to take low and medium calorie liquids at frequent intervals if it's allowed by the type of religious fast.

Training to identify the symptoms of hypoglycaemia, including subtle complaints like difficulty concentrating etc. with appropriate sensitivity towards patients beliefs. Self monitoring of blood glucose with a glucometer wherever feasible and permissible. If postprandial hyperglycemia is a therapeutic challenge, one may shift from rice-based meals to wheat-based food stuffs, which have a lower glycemic index. Nutritional recommendations are often rightly prescribed as part of lifestyle modification (LSM). This includes modification of physical activity to avoid hypoglycemia and dehydration during fasting hours and also stress management.

Conclusion

The benefits of intermittent fasting are beyond that of weight loss. However, it remains to be determined whether people can maintain intermittent fasting for years and potentially accrue the benefits seen in animal models. Furthermore, clinical studies have focused mainly on overweight young and middle aged adults, and we cannot generalize to other age groups the benefits and safety of intermittent fasting that have been observed in these studies.

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UPCOMING CME / CONFERENCES

HORMONE RHYTHM-2024
in 11th & 12th May at Mysuru.

To,