NEWS LINE

KARNATAKA ENDOCRINE SOCIETY

1st Issue | June 2023

THEME - DIABETES MELLITUS

- COMMON MISTAKES IN MANAGING DIABETES IN HOSPITAL
- INPATIENT MANAGEMENT OF HYPERGLYCEMIA
- CURRENT STATUS OF DPP4I AND SGLT2 INHIBITOR IN CLINICAL PRACTICE
- PRESENT AND FUTURE OF INSULIN THERAPY IN DIABETES

Dr. Arpandev Bhattacharyya
President, KES

Dear Colleagues,
It's a great honour for me to be chosen for the post of the President, Karnataka Endocrine Society. I thank all the members of the Society for this opportunity, it is a responsibility to continue the good jobs done by the earlier presidents and at the same time to achieve the mission of our Society. It is only 7 years old but, in that time, we have done quite a significant academic job and most physicians, Paediatricians and Gynaecology and Obstetricians are aware of our work. We need to spread to the awareness to other medical specialities in Karnataka. We have started our Society just before the Pandemic, it is for all of your effort we progressed and continue our academic activities. We are conducting monthly case presentations, annual conferences, in between different updates and also we are planning every three month physical meeting inviting people across different specialities from our country to present their work. This is also a new initiative the Newsline. Here, we want to print some common topics for our colleagues in different connected specialities so that all of us can learn from each other and thereby we can improve the quality of care we provide for our people. I wish the very best to the Editorial team for their effort and all their future endeavours.
We, Karnataka Endocrine Society will strive to bring to you theme based endocrinology newsletter where we discuss aspects of clinical endocrinology which would make practice better for both you and the people we care for.
Warm regards,
Dr. Arpandev Bhattacharyya

Dear Friends,

We are excited to bring you the first edition of our newsletter, dedicated to the fascinating field of endocrinology in Karnataka.

Karnataka, with its diverse population and unique healthcare challenges, presents an intriguing landscape for endocrinology research and practice. Over the years, significant advancements have been made in the field, empowering healthcare professionals to diagnose, manage, and provide optimal care to patients with endocrine disorders.

One of the key areas of focus has been diabetes mellitus, a chronic condition affecting millions of people across the nation. As the prevalence of diabetes continues to rise, we endocrinologists have been at the forefront of innovative treatments, including personalized management plans, cutting-edge medications, and advanced technologies for glucose monitoring. This relentless pursuit of better outcomes has positively impacted the lives of countless individuals and their families.

As we delve deeper into the world of endocrinology in karnataka, we will explore these and many other exciting developments in the field. We will hear from renowned experts, gain insights into groundbreaking research, and learn about the latest advancements in diagnosis, treatment, and patient care.

We hope that this edition of our newsletter serves as a valuable resource for healthcare professionals, researchers, and anyone interested in the dynamic field of endocrinology in karnataka. Together, let us celebrate the achievements, recognize the challenges, and continue our collective efforts towards improving endocrine health in our state and nation.

Thank you for joining us on this journey of discovery and knowledge.

Warm regards,
Dr. Vageesh Ayyar S., Dr. Chitra Selvan

Dr. Arpandev Bhattacharyya

Dr. Ashwitha Shruti Dass

COMMON MISTAKES IN MANAGING DIABETES IN HOSPITAL

Why are mistakes common?

Hyperglycaemia, be it newly detected or existing, is a dynamic process in Hospital because of many confounding factors. Patients are mentally and physically stressed, they are on other medications, may be on steroids, they are undergoing procedures, their meal is different, physical activity is nil and most importantly the atmosphere in Hospital completely new to them. Because of these unstable and unusual situations of glycaemic state changes and you need constant supervision. Understandably there would be some issues in management of Diabetes in order to get a good glycaemic control which is of extreme benefit for recovery.

We asked members of Karnataka Endocrine Society to tell one mistake he or she found common. We picked the top 15 mistakes mentioned and tried to solve them.

1. Checking sugars at fixed time irrespective of food timing:

The nurses are instructed to check sugars pre meals and/or post meals, sometimes due to lack of communication, the sugars are checked at pre- set time like for example 9am, 1pm, 7pm.

Solution: Fixed timing would be allowed only in patients on TPN or Ryle's tube feeding but not in people who are eating normally. So, clear communication to nurses/supervisors in the ward would be the best solution.

2. Primary team not mentioning steroid titration:

Steroids are notorious in increasing sugars, it becomes very important for the diabetes team to be informed and to be aware regarding the steroid therapy as the treatment can be titrated (Uptitration or down titration) according to the sugars and the dose of the steroid. Unfortunately this important information is missed many times which can cause a delay in good control of sugars.

Solution: Communication between specialities would be the best suggestion.

3. Missing premeal insulin as sugar is 110 mg/dl

The value of 110 mg/dl is considered good control of sugar before food, hence sometimes the attending staff/duty Doctors consider the sugar very good which does not require any insulin, hence deliberately the insulin is missed.

Solution: Continuous Medical/Nursing Education would be the best solution in this situation. All of us need to be very clear that when sugar is good, if we miss Insulin sugar will go up, then you give Insulin. More and more fluctuation will be there. It will be chasing the tail approach which we would always discourage.

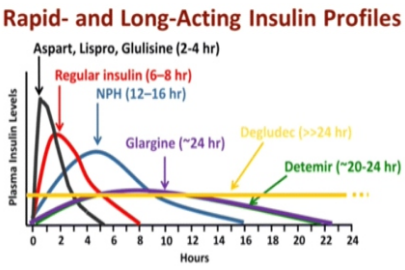
4. Consultation given when sugar is above 400 mg/dl

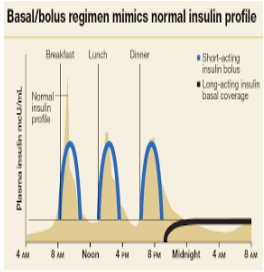
Not uncommonly we see consultation given only when sugar is very high, say above 400 mg%. This again needs a change of our understanding and belief in science that sugar control in hospitals is very important for overall outcome.

Solution: Best is to involve the Diabetes team at admission, so that a clear plan can be chalked out for overall benefit.

5. Using only short acting, no Basal Insulin

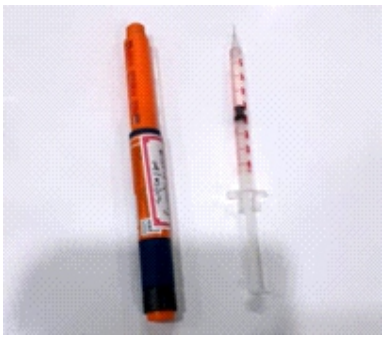
This is one of the common mistakes we see in hospitals. Unfortunately using only short acting insulin is like running behind your own tail as short acting insulin acts only for a few hours. Normally, our pancreas gives 50% Insulin as basal that is being secreted as continuously. Rest 50% Insulin is bolus or short acting or prandial Insulin is available only when we eat and sugar goes up. We in management of Diabetes in Hospital try to emulate the same pattern.





Solution: The best regimen in Hospital will be one basal insulin and three short acting Insulin to get the best diabetes control.

6. Using 40 IU syringe for 100 IU insulin



This is a dangerous and life threatening mistake. We have seen Nurses drawing Insulin from Pen by a syringe with the excuse that a needle for a pen is not available and we need to give Insulin quickly. Not to forget using U40 syringes. This practice can not be acceptable, if you are doing this you are giving two and half times more Insulin, in place of 10 units you are giving 25 units, which can easily be life threatening. If we are using pen we should use pen only, no substitute.

Solution: Continuous Medical/Nursing Education would be the best solution in this situation.

7. Insulin pen and vial, both have been indented, confused

This is a correctable factor at the local level, it is our duty to make nurses, who are in the forefront of Diabetes management in the hospital, aware of all the insulin available in the Hospital, their name and specification. Time to time we need to take classes/CMEs to continue the best quality of care. These types of activities will have to be a continuous process as nurses will change.

Solution: Continuous classes/ CMEs. Also, we can make a huge change that we do not use Syringes and bottles at all in some places, say for example corporate Hospitals and use ONLY syringes and bottle in remote places and also economically privileged areas.

8. Premix ordered in place of Plain Insulin

This is a mistake made by both nurses and from the pharmacist, when a prandial insulin or bolus Insulin has been requested by Doctors, premix Insulin has been dispatched instead. So when the diabetes team is called for the insulin dose which is needed to be given to the patient, there will be a mistake.

Solution: We need to be clear in communication and also we can double check before giving Insulin. Also our team should be clear what Insulins are available in the local pharmacy.

9. Sliding scale Insulin ordered

Sliding scale is commonly written IV or SC route. We strongly believe sliding scale is not worth it and sometime can be dangerous, it leads to fluctuating hypo- and hyperglycemia. It is like chasing the tail, it does not improve overall glycaemic control. Most of the time using sliding scale basal Insulin is omitted. The scientific BBR or premixed insulin would be more appropriate according to the patient's requirement.

Solution: We need to educate our junior medical team not to use a sliding scale, we can use a corrective scale on top of a written dose when sugars are high, this is called corrective scale.

10. Continuing OAD along with Basal Bolus Regimen insulin

OAD can be continued but it is important to be aware about the patient's nutritional status, hence if the team is not been made aware of the nutritional status for example if the patient is on liquid diet and the patient is post-operative and the patient's intake is not adequate, continuing the OAD can lead to hypoglycaemia. Therefore it's important to have thorough information regarding the patient.

Solution: We need to educate our junior team to communicate well with the patient and nursing team on the complete medications list given in the hospital.

11. Not giving Insulin with liquid diet

As mentioned above regarding liquid diet, it mostly depends on the post-operative status or if the patient is on chemotherapy or if the patient's intake is not adequate. Since the nurses/ junior doctors assume the intake may not be adequate like the solid food and they avoid insulin which then leads to hyperglycemia. It should not be forgotten that juices available in the market in tetra packs do come under liquid diet.

Solution: Insulin is needed according to the patient's glycemic state which can be given through IV fluids. A protocol like the GIK regimen can be implemented in the wards with clear communication by the diabetic team to the nursing team.

12. Not respecting Electrolyte imbalance in Diabetes treatment

Monitoring electrolytes is as essential as sugars, for example in the case of consistent hyponatremia and hypoglycemia episodes, it is important to rule out hypocortisolism, so the main issue is resolved. We need to keep a keen watch over the electrolytes not only during the post-operative state but at all times also. It is essential to monitor the patient's medications list as it can cause drug induced dyselectrolytemia. When sugar is very high you get falsely low serum Sodium, this is called pseudohyponatremia. Most important thing in this situation is not to try to correct hyponatremia by hypertonic saline.

Solution: Regular monitoring of electrolytes is needed for the complete care of the patient.

13. Consult sent just before discharge

This tends to occur when the patient is admitted for a short period either for a surgery or a procedure when the consult is raised at the time of discharge. The diabetes treatment is better managed when the sugars are monitored for a minimum 24 hours to understand the patient's sugar fluctuations and thereafter offer the best line of treatment.

Solution: It would be better to raise the consult at the time of admission

14. Panic from ICU as GRBS is low in shock patient

ICU deals with critical patients, some of whom will have very low BP and in a state of peripheral circulatory failure. In this situation due to less peripheral blood flow sugar checked by glucometer will be falsely low.

Solution: In similar situations we need to use venous blood sugar, most of these people will have a central line. This can be continued till circulatory failure improves, after that we can continue our routine practice.

15. IV Insulin infusion stopped before giving SC Insulin

This is a very common mistake we find in the ward when IV Infusion is stopped depending on the clinical situation but SC Insulin is not given before disconnecting the IV insulin. IV Insulin works for 3-5 min, so we need to give the first dose of SC Insulin 30-60 min before stopping the Infusion.

Solution: We need to make aware the juniors and seniors managing diabetes in Hospital to do the correct practice of giving the sc Insulin before switching off the IV Infusion.

It is clear from the above details that we need to communicate with everyone involved in the management of Diabetes in Hospital: Nurses, dietitians, families of the patients, pharmacists, radiology and surgical colleagues, junior and senior Doctors. Talking to each other, making a team for managing Diabetes is the way forward.

Dr. Sphoorti P Pai

Dr. Praveen Devarbhavi

INPATIENT MANAGEMENT OF HYPERGLYCEMIA

> “Needles are no big thing.
> The hard part is the constant high-stakes judgement call”
>
> **- Mother of a child with Type 1 Diabetes**

Diabetes is the new storm which has engulfed India. India is dubiuously renowned as the “diabetes capital of the world”. The latest article from ICMR-INDIAB study published in The Lancet Diabetes and Endocrinology estimates India has 101 million people living with diabetes, which is considerably higher than the previous estimates. This translates into a huge burden of diabetes-related complications and end-organ damage. About one in four patients admitted to hospital has diabetes. About 30% of diabetics require two or more admissions to hospital in a year. Hence it is very important to address hyperglycemia in hospitals as it adds to longer hospital stays, poor outcomes and increased cost burden.

Definition of hyperglycemia in hospital?

Hyperglycemia in hospital is defined as blood glucose level more than 140mg/dl. It can be either pre-existing diabetes (on treatment or HbA1c >6.5%) or “stress hyperglycemia” where the HbA1c levels are <6.5% without any history of pre-existing diabetes.

How does hyperglycemia affect outcomes of a hospitalized patient?

Whether it is new onset hyperglycemia or pre-existing diabetes, either can have worse outcomes in admitted patients. Studies have demonstrated higher infection rates, higher inflammation markers and cytokines, poor cardiovascular outcomes, longer hospital stay and increased costs in patients with hyperglycemia in hospital.

How to choose antihyperglycemic agent in hospital?

There are many challenges faced in a hospital setting. Diet may be inconsistent, patients may have “nil by mouth” or “NPO” orders in patients undergoing procedures. Parenteral and enteral nutrition formulas containing high concentrations of dextrose may be used. Patients may

have medications like steroids and vasopressors which can directly induce hyperglycemia. Stress and infections also can cause hyperglycemia due to increased cortisol and other stress hormones. Insulin is the preferred agent for most patients in hospital. Mode of administration can be subcutaneous in non-critically ill patients and intravenous infusions in critically ill patients. There are many insulin infusion protocols used in the ICU settings, however the protocol used does not matter if the instructions are clear, and the nursing staff understand the protocol clearly. Once the patient is stable hemodynamically, able to take orally, and requiring a stable IV insulin infusion rate, they can be switched over to subcutaneous insulin therapy. The total daily dose requirement can be calculated from the stable IV insulin infusion rate over last 6 hours multiplied by 4. 80% of the calculated dose can be started as subcutaneous insulin divided as 50% basal and 50% bolus insulin. If starting subcutaneous insulin for non-critically ill patients, dose can be started based on weight. 0.2-0.3U/kg for insulin sensitive or elderly individuals; 0.4U/kg for patients with moderate hyperglycemia; 0.5U/kg for insulin resistant individuals or those with severe hyperglycemia. Correctional doses can be added to the scheduled basal-bolus regimen. It is irrational to use "sliding-scale insulin" therapy as there is a mismatch between mealtimes and insulin doses. This regimen is noted to have high glycemic variability with episodes of hyperglycemia and hypoglycemia which can be harmful.

Non-insulin therapies in hospitalized patients:

Metformin

Needs to be stopped in patients with high risk of lactic acidosis like patients undergoing iodinated contrast imaging or arterial contrast injections with low estimated glomerular filtration rate (eGFR), renal or liver dysfunction, sepsis, hypoxia, shock and acute heart failure. In other patients it can be safely used.

Sulfonylureas (SU)

These agents are avoided as they can cause prolonged hypoglycemia sometimes. The UK guidelines recommend using sulfonylureas in steroid induced hyperglycemia. Other guidelines do not generally recommend SU.

Pioglitazone

It can cause fluid retention and needs to be avoided in patients with heart failure and reduced eGFR. **DPP4 inhibitors**

Dipeptidyl peptidase inhibitors are safe to be used in patients with mild to moderate hyperglycemia. They do not cause hypoglycemic episodes and have few adverse effects. Newer studies have shown they are safe to be used in hospital settings in non-critically ill patients.

GLP1 receptor agonists

Studies have shown that exenatide and liraglutide can have better glycemic control in admitted patients with lesser incidence of hypoglycemia. However, they can cause gastritis and reduced gastric emptying and may have to stopped if gastrointestinal side effects are severe.

SGLT2 inhibitors

These agents can cause fluid loss and can precipitate euglycemic ketoacidosis especially in patients who are ill or have the additional stress of surgery. They are also avoided if the patients are admitted with urinary tract infections and genital mycotic infections.

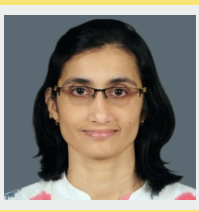
Diabetes technology in inpatient hyperglycemia management

The older guidelines recommended using only point-of-care (glucometer) glucose testing, however with the advent of diabetes technology, continuous glucose monitoring systems (CGMS) are now being used in hospital settings also. Studies have shown better glycemic control with lesser hypoglycemia when used in hospitals. Cost is the major concern in resource poor settings. In critically ill patients, CGMS may not be reliable as it measures interstitial fluid glucose levels and equilibrium with blood glucose may not be attained in conditions with reduced perfusion. Insulin pumps are also being used in hospitals when expertise to adjust insulin pump rates are available. When patients on insulin pumps get admitted it is mandatory to rule out pump dysfunction before continuing insulin pumps in hospital. Switching over to subcutaneous therapy is prudent before stopping pump, if insulin pumps are to be discontinued. Computer app-based infusion algorithms are available to adjust insulin rates in wards and some studies have shown better glycemic control with minimal hypoglycemia when such protocols are used.

In a nutshell:

Hospital settings have some barriers to overcome when managing hyperglycemia. It is important to have at least one glucose reading in hospital when any patient is admitted so that new onset hyperglycemia is not missed. All factors affecting glycemia in hospital settings must be taken into consideration before deciding on therapy or protocols. It is also necessary to adjust doses for the changing scenarios in patients' condition. Diabetes technology can be used whenever expertise is available, and patients are willing to bear the costs as studies have shown they can lead to better glycemia management. Educating all diabetic patients in ward is of utmost importance and a structured diabetes education program should be in place whenever possible with the help of a diabetes educator. The journey from admission to discharge can be smooth if the treatment plan is effectively communicated with the "team" of caregivers and patients' family.

> "Insulin does not belong to me.
> It belongs to the world."
>
> **-Dr. Frederick Banting**



Dr. Akhila B. P. **Dr. Sowrabha Bhat** **Dr. Ganesh H K**

CURRENT STATUS OF DPP4i AND SGLT2 INHIBITOR IN CLINICAL PRACTICE

Dipeptidyl peptidase 4 (DPP-4) inhibitors:

DPP-4 inhibitors (DPP4i) are a group of antihyperglycemic medications used to manage type 2 diabetes mellitus. These drugs act through incretin hormones, which are gut hormones responsible for glucose homeostasis after oral food intake. The first DPP4i approved by the FDA was sitagliptin, which was followed by vildagliptin, saxagliptin, alogliptin, and linagliptin. Other DPP4i available worldwide are anagliptin, gemigliptin, teneligliptin (2012); evogliptin, omarigliptin, trelagliptin (2015); and gosogliptin (2016). While their binding characteristics and pharmacokinetic properties vary, all DPP4i are orally active, selective for DPP-4, have high affinity for the enzyme DPP-4 with similar clinically efficacy for HbA1C reduction.

Major route of drug elimination is renal for sitagliptin, vildagliptin, alogliptin

and saxagliptin ; hepatobiliary excretion is predominant for linagliptin, while for teneligliptin percentage excretion is 45.4% in urine and 46.5% in feces. Thus In patients with any degree of renal impairment linagliptin and teneligliptin can be administered without dose modification. For sitagliptin in mild renal impairment (creatinine clearance ≥ 50ml/min/m2) there is no need for dose adjustment, in those with moderate (creatinine clearance 30 – 50ml/min/m2) and severe renal impairment (creatinine clearance <30ml/min/m2) sitagliptin dose of 50mg and 25mg respectively may be given. For Vildagliptin, dose of 50mg BD can be given in mild renal impairment; and 50mg OD can be administered in moderate to severe renal impairment.

In patients with chronic liver disease, no dose adjustment is needed for linagliptin and saxagliptin. Despite hepatobiliary excretion studies showed mild, moderate or severe hepatic impairment did not result in an increase

in linagliptin exposure after single and multiple dosing compared with normal hepatic function. Sitagliptin and teneligliptin can be given in mild to moderate degree of hepatic impairment, while these drugs are not studied in those with severe hepatic dysfunction. Vildagliptin should be better avoided given in any degree of liver dysfunction.

Cardiovascular outcome trials (CVOT) like TECOS (Sitagliptin) and CAROLINA (Linagliptin) showed non-inferiority. While no CVOTs are available for vildagliptin and teneligliptin, ventricular diastolic function studies for these drugs suggested that the increased left ventricular (LV) volumes observed did not result in increased LV wall stress. SAVOR-TIMI 53 trial for saxagliptin showed a significant 27% increase in relative risk for heart failure related

hospitalization (HHF). Alogliptin in EXAMINE trial showed a non-significant numerical increase in HHF, which reached significance (76% increase) when looking only at subgroup of patients without baseline heart failure.

A major advantage of DPP4i is having neutral effect on weight and insignificant risk of hypoglycemia. ADA 2023 lists DPP4i as intermediate efficacy and weight neutral oral anti-diabetic medication. The results of VERIFY trial which is a randomized, double-blind Phase IV study, supports an early initiation of combination therapy strategy of vildagliptin (50 mg, twice daily) with metformin (1000–2000 mg, daily) over metformin alone in newly detected diabetes mellitus, as patients on combination therapy

met the primary endpoint with a statistically significant 49% reduction in the relative risk for time to initial treatment failure (HbA1c >= 7.0% twice, consecutively, 13 weeks apart), versus metformin alone (HR: 0.51, 95% CI [0.45, 0.58]; P<0·0001).

Some of the adverse events of special interest are angio-edema although mild, may be attributed to DPP4i especially when co-prescribed with ACE inhibitors since DPP4 and ACE are involved in substance P metabolism. Although DPP4 (CD 26) is expressed on lymphocytes, immune related changes and infections are not seen to increase since Binding to the catalytic site does not affect binding on other sites of CD26. A meta-analysis data from the CVOT for pooled DPP4i showed increased RR of acute pancreatitis vs placebo, but absolute risk increase was low (0.13%) and no causal association could be established. More than 10 years of postmarketing surveillance did not suggest an increased risk of cancer with DPP4i therapy. Since development of drug-induced carcinogenicity takes a long time, exposure during RCTs is unlikely to uncover such risks. Pharmacovigilance studies have shown bullous pemphigoid lesions seen increasingly with Increasing age. Hence monitoring for skin lesions is recommended. A warning of arthralgia/severe joint pain has been added to the labels of DPP4i. A special caution is required in the administration of teneligliptin to patients who are prone to QT prolongation.

Thus, DPP4i provide a safe and effective option as a second line of choice in patients with diabetes, which can be considered as first line when a weight neutral option is required as monotherapy or in combination with metformin.

SGLT2 (Sodium Glucose Cotransporter) Inhibitors:

SGLT2 Inhibitors are a relatively new class of oral anti-diabetic agents that act by inhibiting SGLT2, a high-capacity, low-affinity transporter in the early segment of the proximal convoluted renal tubule. Under physiologic conditions, SGLT2 is responsible for reabsorption of 90% of the glucose filtered at the glomerulus, with the remainder being transported back into the systemic circulation by SGLT1, which is located in the distal segment of the proximal convoluted tubule. SGLT2 inhibition leads to glycosuria and lowering of blood glucose becauseSGLT1, a low-capacity, high-affinity transporter cannot reabsorb all of the filtered glucose. Excretion of 60–80 g of excess glucose corresponds to 240–320 kcal of energy loss from the body, promoting weight loss. Improvement of obesity/overweight, especially abdominal fat accumulation, promotes amelioration of insulin resistance and results in improvement of metabolic parameters such as blood pressure, lipid profile, and serum uric acid level. Thus, an insulin-independent mechanism of action and additional benefits make them unique.

As SGLT1 is responsible for glucose absorption in the small intestine, SGLT2 inhibitors with low SGLT1/SGLT2 selectivity such as canagliflozin have been shown to suppress postprandial glucose excursion and increase glucagon-like peptide 1 (GLP-1) secretion in addition to increasing urinary glucose excretion.

The most important SGLT2 inhibitors currently in use in India are empagliflozin, dapagliflozin, canagliflozin and remogliflozin. Remogliflozin was approved in India in 2019 after a phase 3 trial proved its efficacy and safety in comparison to dapagliflozin. However, long term safety and efficacy data especially on cardiovascular and renal outcomes are currently lacking for remogliflozin.

A meta-analysis of 45 clinical trials showed that treatment with SGLT2 inhibitors results in an HbA1c reduction of 0.79% with monotherapy and 0.61% with add-on therapy to other glucose-lowering agents in patients with T2DM. They also reduced body weight by 1.7 kg, and systolic and diastolic blood pressure by 4 and 2 mmHg respectively, serum triacylglycerol level by 1–9%, serum uric acid level by 0.3–0.9 mg/dL, and increase in serum HDL-cholesterol by 6–9%. Although found to increase LDL-cholesterol by 2–6% in a study, the more atherogenic small dense LDL-cholesterol was reduced while the less atherogenic large buoyant LDL-cholesterol was increased by 12-week treatment with dapagliflozin.

The risk of hypoglycemia is generally low but still present, especially when combined with insulin or an insulin secretagogue. A reduction in the dose of insulin is recommended when SGLT2 inhibitors are co-administered with insulin, although the insulin dose reduction needs to be not greater than 20 % of the total daily insulin dose in order to prevent euglycemic diabetic ketoacidosis.

The EMPA-REG OUTCOME trial showed that treatment with empagliflozin resulted in significant reduction in the primary endpoint [3-point MACE (Major Adverse Cardiovascular Events); a composite of CV death, non-fatal myocardial infarction and non-fatal stroke] by 14% and especially CV death by 38%. Also significantly reduced was the incidence of hospitalization for heart failure by 35%. Renal events including a composite of progression to macroalbumiuria, doubling of serum creatinine level, initiation of renal-replacement therapy, or death from renal disease were significantly reduced by 39%. The subsequent CANVAS/CANVAS-R trials revealed similar cardiovascular and renal benefits for canagliflozin, thus proving that these were a class effect of SGLT2 inhibitors. The CREDENCE trial showed reno-protective effects further extended to diabetics with chronic kidney disease (CKD).

As per ADA/EASD guidelines, the use of SGLT2 inhibitors is, currently recommended for patients with a high risk of or established atherosclerotic cardiovascular disease (ASCVD) and those with CKD or heart failure. Guideline directed medical therapy for patients with heart failure with reduced ejection fraction (HFrEF) includes SGLT2 inhibitors. In the EMPEROR-Preserved trial, SGLT2 inhibitors have been found to benefit patients with heart failure with preserved ejection fraction (HFpEF), irrespective of their diabetic status and hence approved for use in these patients.

According to the consensus guidelines by the American Diabetes Association (ADA) & Kidney Disease Improving Global Outcomes (KDIGO), SGLT2 inhibitors with established kidney or cardiovascular benefit is suggested for patients with type 2 diabetes mellitus, CKD, and eGFR >20 mL/min/1.73 m^2. Once initiated, the SGLT2 inhibitors can be continued at lower levels of eGFR. Individual patient factors should be considered before starting the therapy in case of discrepancy. For patients with diabetic kidney disease, using an SGLT2 inhibitor in patients with urinary albumin

>200 mg/g creatinine is advised to reduce CKD progression and cardiovascular events. However, patients with hypovolemia are at risk for the development of acute kidney injury and volume status needs to be optimised before initiating therapy.

Side effects of SGLT2 inhibitors include genito-urinary infections, dehydration, increased risk of falls and fractures, sarcopenia, Fournier's gangrene and euglycemic DKA. Although the risk of amputation is lower than previously communicated by the FDA, it is prudent to exercise caution in the use of SGLT2 inhibitors in patients with peripheral vascular disease, neuropathy, history of diabetic foot ulcer, and previous history of amputations.

SGLT2 inhibitors, with their cardiorenal and metabolic benefits and acceptable side effect profile, have emerged as a gamechanger in the management of diabetes. They can be used as preferred first line agents in overweight/obese patients who had ASCVD in the past or who have multiple risk factors for developing ASCVD.

Dr. Manjunath P R

Dr. Ganavi. Y. P

PRESENT AND FUTURE OF INSULIN THERAPY IN DIABETES

Present and future of insulin therapy in diabetic patients

- The first therapeutic use of insulin for management of type 1 diabetes was in 1921 by Banting and Best.The year 2021 marks the 100th year of insulin discovery ,since then there are significant advances which took place in the field of insulin therapy,aiming to achieve optimal glycemic control along with decreased diabetes-related complications. Inspite of all the developments, there are still several challenges in insulin therapy, such as increasing treatment flexibility, reducing iatrogenic hypoglycemia and optimizing patient quality of life.Newer insulin analogs ,alternative routes of insulin administration, closed-loop technology are few of the innovations to overcome the challenges and change the landscape of diabetes management.

Evolution of insulins:

- After the first clinical use of 'regular' insulin for patients, the pancreatic extract was further purified, the source of insulin moved to pork and later beef pancreas, and the concentration was increased from the original commercially available U-5 insulin to U-10, U-20, U-40 and U-80 preparations. Later, U-100 became the most common insulin preparation used in early 1970s. Later from animal sources insulin preparations moved on to human insulin produced through recombinant DNA technology.These insulins were still zinc-based formulations with slower pharmacokinetic profiles than natively secreted insulin.
- The 1993 publication of the Diabetes Control and Complications Trial and 1998 United Kingdom Prospective Diabetes Study demonstrated definitive relationships between glycemic control and microvascular complications and showed that lower A1cs were associated with higher rates of severe hypoglycemia. These observations spurred efforts focused on improving exogenously administered insulin's pharmacokinetic and pharmacodynamic properties (absorption rate, time to peak and duration of action). This has been accomplished over time using recombinant DNA technology and genetic engineering, and adding excipients.
- Three main techniques were developed to change the rate of insulin hexamer to monomer conversion: 1) Alteration of the insulin amino-acid sequence,2) Addition of fatty acid components that modify the link between insulin hexamers and impact their binding with albumin in the bloodstream 3) Use of additives that influence insulin absorption rate.

- **NEWER GENERATION INSULIN THERAPY**
- Rapid insulins are primarily used to control postprandial glucose excursions. In the 1990s and early 2000s, three insulin analogs (aspart, lispro and glulisine) were developed through amino acid sequence modifications. This rendered their pharmacokinetic profiles more similar to endogenous prandial secretion, with a faster onset of action, an earlier peak effect and a reduced duration of action.
- Hepatoselective insulins are thus being developed to restore the normal portal-peripheral insulin gradient. Ex: PegLispro, which is comprised of insulin lispro linked to a hydrophilic polyethylene glucose polymer, exhibits hepatic selectivity . Drug was discontinued in view of liver and lipid abnormalities .
- Later ultra-rapid aspart was developed with addition of niacinamide (a form of vitamin B3) and L-Arginine (an amino acid) to insulin aspart for faster hexamer dissociation and monomer absorption.
- **Ultra-long basal insulin:**
- Early attempts at lengthening insulin time-action profiles with protamine and zinc in the 1930s (e.g., NPH insulins), followed by altered amino acid sequences (e.g., glargine) in the 2000s, marked important turning points in the quest to establish the ideal basal insulin.
- Currently Insulin degludec is the longest-acting insulin analog available on the market produced with the addition of a fatty acid/glutamic acid side chain which forms a soluble multihexameric depot after injection.
- **Concentrated insulin therapy :**
- Concentrated insulins possess a reduced injection volume and, in some cases, a different pharmacokinetic profile,can be used in patients requiring higher insulin doses.
- Ex: Regular insulin U-500 , insulin glargine U-300, degludec U-200 and lispro U-200.
- Although the exact mechanism underlying the pharmacokinetic profile is not fully understood, it is hypothesized that the volume of subcutaneous depot may impact the rate of hexamer degradation and monomer absorption.

- **Future of insulins:**
- Newer insulins in pipeline:
- Insulin lispro-aabc – produced by adding a local vasodilator (treprostinil) and an inhibitor of hexamer formation (citrate) to insulin lispro.
- Once-weekly insulin icodec is also in development. It was designed with the substitution of three amino acids to prevent enzymatic degradation and the addition of a C20 fatty diacid to promote albumin binding, which allows for an even flatter profile and an extended half-life.
- Two other methods of hastening insulin absorption are being investigated:

  1) Insulin-PH20 is produced by adding hyaluronidase enzyme to insulin lispro to enhance its subcutaneous permeability

  (2) BioChaperone technology is a molecular delivery system that forms a complex with insulin lispro, protects it from enzymatic degradation and promotes faster hexamer to monomer conversion.

- **Ultra-stable insulin:**
- Single-chain insulin analog (SCI-57): This is a 57-residue single-chain insulin analog (SCI-57) that resist thermal fibrillation(amyloid fibrils are formed when cold chain not maintained) in vitro and exhibits equivalent biological properties than native insulin in vivo animal models.
- **GLUCOSE-RESPONSIVE INSULIN :**
- These insulins were developed which can respond to varying blood glucose levels.
- Molecular glucose-responsive insulin:
- Polymer-based system consists of insulin molecules contained within a glucose-responsive polymeric matrix-based vesicle composed of glucose-binding proteins (e.g., concanavalin A), glucose oxidase or phenylboronic acid.
- Molecular-based bioconjugation approach involves the introduction of a motif (e.g., phenylboronic acid, glucosamine or mannose) to native insulin which provides it with glucose-responsive properties without the need for exogenous matrices.
- Currently no approved insulin therapies whose bioactivity is regulated by blood glucose levels are available.
- **Mechanical glucose-responsive insulin:**
- The most advanced and promising insulin delivery method is closed-loop insulin delivery systems, also known as the artificial pancreas. They consist of a continuous interstitial glucose monitoring device that detects glucose levels and communicates these values to an insulin pump. This automated pump uses intelligent algorithms to adjust insulin delivery in real time.
- Research is rapidly evolving in this field and aims to establish fully automated closed-loop systems through the addition of other hormones such as glucagon.

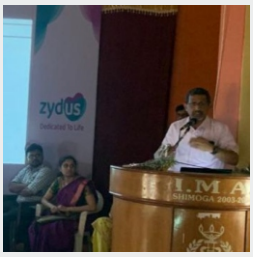
- **ALTERNATIVE ROUTES OF INSULIN DELIVERY :**
- Efforts are being invested into developing alternative routes of insulin delivery. In recent years, two rapid-acting inhaled insulins obtained FDA approval in the United States.Pulmonary bioavailability allows these insulins to control postprandial glucose excursions, but long-term pulmonary safety is still being investigated.
- The oral route is also of significant interest due to its simplicity and because it involves more physiological first-pass metabolism. However, ensuring mucosal absorption of insulin while avoiding enzymatic degradation in the gastrointestinal tract remains a challenge.
- New formulations of oral insulin containing protease inhibitors and mucosal absorption enhancers have ensured these molecules' integrity and bioavailability, leading to some clinical efficacy in phase 2 trials.
- Nevertheless, these non-invasive insulin treatments remain of interest and could represent new paradigms for the future treatment of diabetes.
- **BIOGENERICS :**
- Since insulin production is complex and costly, only a few biosimilar insulins are currently available on the market. The production of further biosimilars should contribute to more affordable costs.

KARNATAKA ENDOCRINE SOCIETY - EVENTS

"ENDOCRINE EXTRAVAGANZA" CME PROGRAM - SHIVAMOGGA

The KES has taken an initiative to conduct CME programs across the state. Shivamogga was one of the places where the **"Endocrine Extravaganza" CME program was jointly conducted by the API Sahyadri-Shivamogga Branch and KES in association with IMA, Shivamogga.** Thanks to the relentless efforts by Dr. Gopal, Secretary, API Shivamogga and Dr. Raksha Rao, Secretary, IMA-Shivamogga, we could bring together the KES, API and IMA for a successful program on 5th March 2023.

As a scientific secretary, I express my gratitude to my seniors Dr. Vageesh Ayyar, Dr. Somashekara Reddy KS and Dr. Praveenkumar Devarbhavi for guiding me, helping me chalk out the interesting sessions and bringing together elite faculty for the program. I thank Dr. Arun, President, IMA-Shivamogga, Dr. Shivaramakrishna, President, API-Shivamogga and Dr. P.K. Pai, Vice-president, API-Shivamogga for being the pillars of support. I am grateful to Dr. Sudeep K, Dr. Mallikarjun V J, Dr. Anusha Nadig and Dr. Vishwanath S, who came from across the state to deliver the impressive lectures. The active participation from all the delegates cannot be undermined for making the event fruitful.The audience appreciated the intricacies in endocrinology discussed during the sessions. Here are some memories from the program...



"HORMONE RHYTHM 2023" 5TH ANNUAL CONFERENCE - BELAGAVI

Karnataka Endocrine Society and Dept of Endocrinology JNMC Belagavi organised 5th annual conference **"Hormone Rhythm 2023" on 6th and 7th may 2023 at JNMC convention center Belagavi.** It was was attended by more than 650 delegates all over Karnataka. Speaker from allover India were invited and was well appreciated by all delegates.

We wish to share some of the memorable movements captured during the conference and hope you to cherish the memories of the same.

UPCOMING CME / CONFERENCES

THYROID UPDATE
in August 2023 at Bengaluru.

ENDOCRINE UPDATE
in September 2023
at J.J.M Medical College, Davanagere.

HORMONE RHYTHM-2024
in May at Mysore.

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(Affiliated to Endocrine Society of India)

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"MANGALORE ENDOCRINE UPDATE - 2023"

The Mangalore Endocrine and Diabetes Society (MEDS) successfully hosted the **"Mangalore Endocrine Update-2023" on June 04, 2023 at the TMA pai convention centre, Mangalore, Dakshina Kannada.** The CME had three sessions (of three topics each), besides the Inaugural and Valedictory sessions. The scientific agenda was an array of carefully selected topics chosen by the scientific committee comprising Dr. Ganesh HK, Dr. Gururaja Rao, Dr. Shrikrishna Acharya, Dr. Shrinath Shetty and Himamshu Acharya. The Endocrine Society Quiz was appreciated well for its technical and academic aspects.

The program was well-attended and the sessions were interactive. An impressive line-up of experts from across south India well-presented the topics. All three sessions were chaired by senior faculty from allied fields. In addition, to the delight of the audience, the discussions were taken to the higher levels thanks to the presence of the stalwarts of Karnataka Endocrine Society Dr. Arpan Dev Bhattacharya, Dr. Vageesh Ayyar and Dr. Somashekara Reddy. The support of sponsors and medical institutions of Mangalore ensured a successful endeavour on that day for MEDS to cherish and carry forward in their future academic assignments.

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