Diabetes India 2022: 12th World Congress of DiabetesIndia

METFORMIN SUPREME POSITION AS A FIRST CHOICE: PROS AND CONS

Dr Meena Chhabra, New Delhi

Based on the medical community's extensive experience and the drug's demonstrated efficacy, safety and low-cost, metformin should remain the "foundation therapy" for all patients with type 2 diabetes, barring contraindications.

Metformin is contraindicated in:

- Patients with severe renal dysfunction (glomerular filtration rate [GFR] <30 mL/min/1.73 m^2).
- Hypersensitivity to metformin and metabolic acidosis. Metformin dosing should also stop on the day of any surgery.
- Discontinue metformin before giving iodinated contrast agents in patients with a GFR <60 mL/min/1.73 m^2, lactic acidosis risk factors.
- Metformin may be restarted after the procedure once the patient's GFR has normalized. Avoid metformin in hepatically impaired or unstable heart failure patients.
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RA) may only be considered as first-line therapy in case of atherosclerotic cardiovascular disease (ASCVD) or high/very high cardiovascular (CV) risk.

RESPONDERS AND NONRESPONDERS TO SGLT2 INHIBITORS AND GLP-1 RECEPTOR AGONISTS: POSSIBLE MECHANISMS AND OPPORTUNITIES

Dr Leszek Czupryniak, Poland

- Aspects of the mechanisms of GLP-1RA-induced weight loss: Weight loss induced by caloric restrictions leads to a compensatory reduction in energy expenditure; Weight loss induced by semaglutide only transiently did so: energy expenditure returned to baseline levels within a week.
- The possible mechanism for (non)-responding to GLP-1RAs are GLP-1 receptor genetic polymorphism, various degrees of receptor response to GLP-1, adaptations in basal metabolic rate, varied CND response to hypothalamus stimulation, early vs. late responders, duration of the history of obesity and increased vs. decreased patient's motivation to lifestyle modification.
- The possible mechanism for (non)-responders to SGLT2 inhibitors is compensatory hyperphagia-varied degree, adaptations in basal metabolic rate and complex hormonal changes due to calorie loss with urine.
- Clinical questions that remain unanswered are: Successful identification of early and late and nonresponders - clinical criteria; Giving up medications in non (late?) responders vs. intensifying therapy; Combination therapy - in whom, in what sequence?

WHAT FUTURE TREATMENTS ARE ON THE HORIZON FOR NAFLD?

Dr Shalini Jaggi, New Delhi

- One in five individuals globally are estimated to have nonalcoholic fatty liver disease (NAFLD). Its prevalence is strongly associated with obesity and metabolic disorders; however, evidence is mounting among nonobese individuals.
- Whilst bland steatosis itself is not harmful, it lays the foundation for the development of nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma. The complex and heterogeneous nature of NAFLD challenges the quest to find the holy grail of treatments.
- So far treatments are generally aimed at directly ameliorating either one of the hallmark characteristics driving NAFLD (steatosis, inflammation and fibrosis) or the gut microbiome. The NAFLD treatment landscape is rapidly evolving as a consequence of our growing understanding of its underpinning mechanisms. Treatments aimed at ameliorating not one, but multiple, features of the condition hold great promise. Several treatments have been tested in clinical trials, and whilst some promising results have been obtained, most have failed to deliver the desired outcome.

- Increasing appreciation of the heterogeneity of NAFLD will enable us to develop more personalized therapies. Whilst the holy grail has not yet been found; step by step, its quest is ongoing and getting closer to the discovery of successful NAFLD treatments.

ARE WE MISSING EVIDENCE-BASED PRACTICE IN DIABETES?

Dr Benny Negalur, Thane, Maharashtra

If we all agree on best practices based on data and research – we can reduce unnecessary care, save money and push people into pathways to yield better results.

- Scientific discovery in recent years has led to important advances in our understanding of the mechanisms that may underlie type 2 diabetes.
- Interventions to increase exercise, reduce weight and control elevated glycemia, blood pressure (BP) and cholesterol levels demonstrated a significant decrease in morbidity and mortality. Many barriers to the adoption of evidence into clinical care at the community level exist. Diabetes translational issues are diverse and complicated. No single best practice is appropriate for all patients and practitioners. Tailoring to patients and customizing to settings is necessary.
- Real-world translation requires flexibility to deal with pragmatic issues such as provider time constraints, reimbursement and system problems.

DIABETES CARE: TIME TO CONCENTRATE ON COMPREHENSIVE CARE

Dr SR Aravind, Bengaluru

- Diabetes mellitus is one of the most serious chronic illnesses in the world due to its prevalence, economic and social effects, and negative impact on the quality of life of the affected people.
- The diagnosis implies changes in life habits especially related to feeding, physical activity and constant self-care, requiring greater personal autonomy.
- Complications - both microvascular and macrovascular can lead to poor quality of life. Physically, mentally and economically draining leading to both patient and family suffering.
- Mysteries of diabetes are evolving and will continue - continuous knowledge update is a must.
- The failure of clinicians to intensify therapy when clinically indicated has been termed "clinical inertia".
- Education and comprehensive care throughout life are the keys to good health in people with diabetes.
- Education is 'hand holding' the patient for life.
- Diabetes care is teamwork, turning out to be cardiometabolic, renal and vascular in approach.
- The basic minimum care team in diabetes comprises doctors, patients, dieticians, diabetes educators and nurse educators.
- The success of your diabetes management depends on:
  - Guideline-directed medical therapy
  - Evaluate practice pattern, patient segment, and plan the process
  - Evaluate patients for micro- and macrovascular complications
  - Educate each patient, each visit with patience
  - Practice care with empathy - learn soft skills and communication
  - Contribute to research, audit your practice
  - Be accessible-affordable-accountable
  - Never chase success - chase satisfaction.

ARE WE MIGRATING FROM SMBG TO CGM?

Dr Banshi Saboo, Ahmedabad

- Self-monitoring of blood glucose (SMBG) measurements do not capture the post-meal spike while continuous glucose monitoring (CGM) captures post-meal spike and glycemic excursions across the day.
- CGMs provide information about the glucose concentration as well as trend information about the direction and rate of changing glucose concentrations.
- Guidelines recommend the use of CGM in diabetes management.
- Numerous randomized controlled trials have demonstrated benefits from using real-time CGM over SMBG, including a lower A1c and/or reduced hypoglycemia.

FOCUS ON TIR THROUGH CGM TO TARGET BETTER CLINICAL OUTCOMES IN DIABETES

Dr Manoj Chawla, Mumbai

- There are many faces of A1c, though HbA1c is still a standard measure for glycemia, they don't provide a complete picture.

- Ambulatory glucose profile (AGP) carries metrics data of time-in-range (TIR) and is crucial in SMBG, CGM, etc.
- % TIR and HbA1c have a broad correlation between a range of subjects, ages and technologies across 18 subjects.
- For every absolute 10% change in % TIR, there is approximately a 0.8% reduction in HbA1c along with a 6.4% risk reduction for abnormal carotid intima-media thickness (CIMT).
- TIR and glycemic variability (GV) are mathematically interrelated; however, they are not interchangeable.

A SILVER LINING IN THE ARMAMENTARIUM OF DIABETES THERAPY: THE BIRTH OF THE WORLD'S FIRST "PEPTIDE IN A PILL"

Dr Rajiv Kovil, Mumbai

- Peptides are challenging compounds and require engineering to optimize their *in vivo* performance.
- Peptide analogs can be designed to offer improved stability and prolonged $t_{1/2}$, while a formulation approach can facilitate improved absorption.
- Absorption of oral semaglutide takes place in the stomach and requires coformulation with SNAC.
- The mechanism of absorption is shown to be compound-specific, transcellular and without any evidence of an effect on tight junctions.
- The development of "peptide in a pill-oral semaglutide" represents an advancement in treatment possibilities for chronic diseases by transforming injectable therapies into tablet-based oral formulations.

CARDIOVASCULAR OUTCOME TRIAL REQUIREMENTS SHOULD NOT BE ABANDONED

Dr Rajeev Chawla, New Delhi

- The requirement to test one new drug in class should be tested in cardiovascular outcome trial (CVOT) to give assurance and evidence to treating physicians about its efficacy and safety.
- It should be noted that in referring to cardiovascular disease (CVD), we include not only macrovascular but also microvascular morbidity.
- Both are equally important from a CV outcome point of view.
- New and existing glucose-lowering therapies should be evaluated for their overall effects on vascular health, the various CV phenotypes (e.g., heart failure), and specific vascular complications such as amputations.
- CVOTs have sensitized diabetes care providers to the opportunities for multifactorial and comprehensive diabetes care, including CV risk reduction.
- Some of the more recent CVOTs have embraced comprehensive cardiorenal primary endpoints, originally proposed by investigators from earlier trials.
- CVOTs have still a long way to go. Primary intervention trials in lower-risk populations could determine whether diabetes medications offer CV protection for those who do not yet have CVD.

25 YEARS OF ACARBOSE IN INDIA

Dr BM Makkar, New Delhi

- In Indian patients considering a carbohydrate-rich diet, acarbose works by inhibiting alpha-glucosidase causing a delay in intestinal absorption of carbohydrates along with decreasing insulin need.
- The structural uniqueness of the acarbose reduces postprandial plasma glucose (PPG) via an insulin-sparing mechanism and facilitates its entry into the large intestine.
- Several studies have proved that acarbose reduces Hb1Ac by 0.8% along with a reduced risk of progression from prediabetes to type 2 diabetes.
- Acarbose is recommended by various international communities owing to glucose-lowering efficacy across a broad range of patients, regardless of BMI, HbA1c, duration of diabetes, insulin resistance, condition of β cells, age, etc.

DPP-IV AND ORGAN PROTECTION: EVIDENCE-BASED CHOICES

Dr SK Sharma, Jaipur

- Dipeptidyl peptidase-4 (DPP-4) inhibitors beyond its well-established actions on the pancreas GLP-1 further exert direct effects on the heart, vessels and kidneys, mainly via the GLP-1 receptor.
- Preclinical evidence suggests that DPP-4 inhibitors may be beneficial in settings of acute renal failure and chronic kidney diseases (CKDs) such as diabetic nephropathy, but also cardiac diseases such as myocardial infarction and heart failure.
- DPP-4 inhibitors raise the possibility of a direct renoprotective effect independent of improvements in glycemic control.

- DPP-4 inhibitors demonstrate clinically meaningful benefits in clinical phase 3 and 4 trials in the treatment of acute kidney failure, chronic kidney failure and acute myocardial infarction as well as heart failure.

MECHANISM OF β-CELL DYSFUNCTION IN T2DM

Dr Om Lakhani, Ahmedabad

- Over 50% of β-cell function is lost at the time of diagnosis along with a 4% to 5% reduction every year in type 2 diabetes patients.
- Beta-cell impairment is the key to the pathogenesis of type 2 diabetes.
- In comparison to the insulin resistance in a prediabetic patient, diabetic patients have both insulin resistance and β-cell dysfunction as insulin secretion is a cumulative factor of β-cell mass and its function.
- Preservation of β-cell is the key to preventing progression from prediabetes to type 2 diabetes and further disease progression in type 2 diabetes patients itself.

TIMELY INTERVENTION IN T2DM: FOCUS ON SGLT2–DPP-4 INHIBITOR COMBINATIONS

Dr AG Unnikrishnan, Pune

- The sequential treatment approach is often compounded by substantial clinical inertia to timely treatment intensification. Substantial clinical inertia exists at each sequential intensification step.
- At HbA1c 8.0% to 8.5%, HbA1c-lowering is slightly greater with DPP-4 inhibitors than with SGLT2 inhibitors as an add-on to metformin. SGLT2 inhibitors are associated with larger HbA1c levels.
- DPP-4 inhibitors moderate the risk of genitourinary tract infections associated with SGLT2 inhibitors.
- In cases of HbA1c ≥8.0%, dual DPP-4 inhibitors-SGLT2 inhibitors add-on therapy to metformin should be considered to help more patients achieve glycemic targets.
- Real-world evidence with empagliflozin and linagliptin FDC conducted across India involving 1,232 T2D patients showed a significant reduction in HbA1c, fasting plasma glucose (FPG), PPG, weight and BP.

UNLEASHING THE POTENTIAL FOR RENAL PROTECTION WITH SGLT2 INHIBITION: A CLINICAL PERSPECTIVE

Dr NK Singh, Dhanbad

- SGLT2 inhibitors are an important weapon in our arsenal against not only type 2 diabetes but also the conditions that we encounter that go hand-in-hand, including CKD and CVD.
- Frontline clinicians should initiate SGLT2 inhibitors for patients with type 2 diabetes and diabetic kidney disease who have an eGFR of at least 30 mL/min/1.73 m^2.
- Deferring initiation of SGLT2 inhibitors to a specialist (a nephrologist or endocrinologist) will result in a faster progression of diabetic kidney disease irrespective of glycemic control, and it is crucial to initiate these medications as early as possible.
- Prescribers should be aware of the initial reversible drop in eGFR of approximately 5 to 8 mL/min/1.73 m^2 (up to a 20% drop) in the first 2 weeks after starting SGLT2 inhibitors, which is due to the hemodynamic effects of the drug.
- The use of an SGLT2 inhibitor can slow the decline in GFR, reduce the onset of microalbuminuria and slow or reverse the progression of proteinuria.

LATENT AUTOIMMUNE DIABETES IN ADULTS

Dr Sanjay Reddy, Bengaluru

- Latent autoimmune diabetes in adults (LADA), dubbed type 1.5 D may account for 2% to 12% of all cases of diabetes in the adult population.
- LADA is a form of diabetes mellitus that has characteristic manifestations similar to both type 2 diabetes and type 1 diabetes. Early diagnosis is paramount to inhibiting appropriate treatment and preventing complications.
- New insight into the pathophysiology of LADA explained the slow progression of β-cell destruction.
- Insulin, DPP-4 inhibitors alone or in combination with thiazolidinediones, and GLP-1 receptor inhibitors have shown promising results in controlling glycemic levels and preserving β-cell functions.

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