

DRS - WCPD

DIABETES RESEARCH & SOLUTIONS

11TH WORLD CONGRESS ON PREVENTION OF DIABETES AND ITS COMPLICATIONS

Theme:

Prevention of Diabetes and
Prevention of Complications

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Newsletter

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My Journey with Insulin

Insulin therapy has advanced significantly, offering various analogs to meet the diverse needs of patients with diabetes. Despite the availability of oral hypoglycemic agents, insulin remains the most effective option for managing blood glucose, particularly for those struggling to achieve control with oral medications. Although insulin can cause weight gain, it has a neutral effect on major adverse cardiovascular events (MACE), heart failure (HF), and diabetic kidney disease (DKD).

The DIGAMI trial has shown the cardiovascular benefits of intensive insulin therapy, especially after a myocardial infarction. It has been suggested that insulin-glucose infusion followed by subcutaneous insulin can reduce mortality in diabetic patients post-myocardial infarction, especially in low-risk, insulin-naïve patients. However, common obstacles to insulin therapy include patient apprehensions and the complexity of treatment plans. Some of the tips about insulin initiation for glycemic management include:

- For adults with type 2 diabetes (T2D), insulin therapy options include neutral protamine Hagedorn (NPH) insulin, which can be injected once or twice daily based on individual needs.
- In cases where glycated hemoglobin (HbA1c) is above 9.0%, a combination of NPH and short-acting insulin may be considered separately or as a pre-mixed human insulin preparation.
- Switching to insulin detemir or insulin glargine may be beneficial for those who experience significant hypoglycemia or fail to meet their HbA1c targets with NPH insulin.

Lastly, modern insulin analogs, including rapid, short, intermediate, and long-acting options, offer flexibility in dosing and convenience. However, physicians should confidently prescribe standard insulins and carefully consider using newer analogs without succumbing to external pressures.



Prevention of Heart Failure in Diabetes

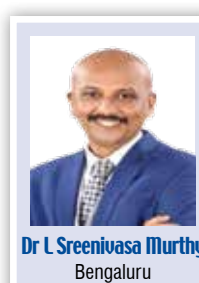
- Human myocytes do not have an endogenous capacity for repair; once dead, they cannot regenerate.
- Preventing HF is critical, as it follows a malignant progression once it sets in and is associated with high mortality and morbidity.
- Serum biomarkers like B-type natriuretic peptide (BNP) >50 pg/mL and N-terminal pro-BNP (NT-proBNP) >135 pg/mL should be included in the assessment of stages A and B of HF.
- The prevention of HF in clinical practice is often neglected, highlighting an urgent need to promote current scientific knowledge on HF prevention in stages A and B.



Lina/Dapa/Metformin FDC: The New Kid on the Block

Approximately 67% of type 2 diabetes mellitus (T2DM) patients in India do not meet their target HbA1c goals. As a multifactorial disease with significant cardiorenal complications, T2DM requires the use of oral antidiabetic drugs that address multiple pathophysiological defects to achieve effective glycemic control.

Delayed treatment intensification in high-risk patients increases the likelihood of myocardial infarction and stroke. Research indicates that early, intensive glycemic control can reduce the risk of both micro- and macrovascular complications. According to the American Diabetes Association (ADA) guidelines, combination therapy is recommended when HbA1c is ≥1.5% above target levels. The fixed-dose combination (FDC) of metformin, dapagliflozin, and linagliptin improves glycemic control and addresses cardiorenal



(Cont'd on pg. 2....)



LADA: A Mystery Solved

- ▣ Latent autoimmune diabetes in adults (LADA) exhibits characteristics of both type 1 and type 2 diabetes mellitus (T1DM and T2DM).
- ▣ Early diagnosis is crucial for initiating the appropriate treatment and preventing complications.
- ▣ Clinicians should consider screening for LADA in patients with T2DM who do not achieve adequate glycemic control despite adhering to therapy.
 - Especially if they are not obese, lack features of metabolic syndrome, or have a personal or family history of autoimmune disorders.
- ▣ Recent insights into LADA's pathophysiology reveal that beta-cell destruction progresses slowly.
- ▣ A C-peptide test, whether basal or after a mixed meal, can be an initial, cost-effective screening tool to identify patients needing further confirmatory testing for islet autoantibodies.
- ▣ Insulin and dipeptidyl peptidase-4 (DPP-4) inhibitors, either alone or in combination with insulin, thiazolidinediones, and glucagon-like peptide-1 (GLP-1) receptor agonists, have demonstrated effectiveness in achieving glycemic control and preserving beta-cell function.



CGM as a Guide for Dietary Interventions



The role of food-based dietary strategies in achieving T2D remission has gained significant attention, particularly with the rise of Mediterranean and plant-based diets. Continuous glucose monitoring (CGM) technology has shown promise in refining diet and lifestyle adjustments, but its application has limitations. Recent editorial critiques highlight that promoting CGM for nondiabetics may lack sufficient evidence and could potentially lead to eating disorders. For newly diagnosed patients reluctant to start medication, CGM can offer valuable insights, helping to reduce instances of hypoglycemia and hyperglycemia. It provides a feedback loop that enhances dietary adherence and overall health outcomes. Studies have demonstrated that dietary responses can vary significantly due to factors such as microbiota and food additives in processed foods.

To optimize the use of CGM, integrating it with personalized dietary guidance can be highly effective. Health care providers can use CGM data to offer tailored meal timing and composition advice, thereby stabilizing blood sugar levels. Practical strategies include:

- ▣ Focusing on one meal at a time and modifying it if postprandial glucose (PPG) is high, such as substituting rice with more vegetables or lentils.
- ▣ Advising patients to keep a food diary to better correlate with glucose spikes from the ambulatory glucose profile.
- ▣ Teaching patients to monitor their time-in-range for motivation.
- ▣ Explaining the impact of exercise and stress on glucose levels.
- ▣ Encouraging experimentation with different diets, such as low-carb or high-protein, or sequencing foods to manage PPG spikes effectively.

(...Cont'd from pg. 1) *Lina/Dapa/Metformin FDC: The New Kid on the Block*

complications, reflecting real-world clinical practices. This once-daily regimen targets a wide range of pathophysiological factors involved in hyperglycemia, improving patient compliance and quality of life.

Key Observations

- ▣ Combination therapy addresses multiple pathophysiological defects, achieving significant HbA1c reduction while minimizing pill burden.
- ▣ Combining dapagliflozin and linagliptin with metformin offers clinically meaningful improvements in glycemic control with better tolerability and safety.
- ▣ Studies have shown that the triple combination of linagliptin, dapagliflozin, and metformin not only provides glycemic efficacy but also enhances cardiorenal safety. Additionally, linagliptin does not require routine monitoring of urine albumin-to-creatinine ratio (UACR) and does not need dose adjustments.
- ▣ The triple combination of metformin, dapagliflozin, and linagliptin can be used safely in patients with an estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m².

Reassuring Hypertension Management with CV Protection in Young

Hypertension is a key risk factor for a range of cardiovascular conditions, such as coronary artery disease, left ventricular hypertrophy, valvular heart disease, atrial fibrillation, stroke, and renal failure. The continuous correlation between blood pressure levels and cardiovascular events blurs the distinction between high normal blood pressure and hypertension, as the cut-off values are somewhat arbitrary. Prevention and treatment of cardiovascular disease should be based on a comprehensive assessment of overall cardiovascular risk, which can be estimated using various models. However, age heavily influences risk categorization. Young adults, particularly women, may not be classified as high-risk despite having several major risk factors, emphasizing the importance of age-adjusted models. These models should evaluate relative risks compared to peers of the same age and incorporate assessments of target organ damage and 24-hour ambulatory blood pressure monitoring.



Key strategies for cardiovascular protection include:

- ▣ Managing dyslipidemia in young hypertensive patients with statins and following aspirin guidelines for primary prevention.
- ▣ Regularly monitor blood pressure at home and in clinical settings, as well as track kidney function, ECGs, and echocardiograms.
- ▣ Addressing barriers such as cost and side effects, utilizing educational strategies, simplified treatment regimens, and mobile apps to enhance patient outcomes can improve adherence.
- ▣ Leveraging digital health technologies, such as noninvasive BP measurement devices and data storage systems, which are expected to play an increasing role in hypertension management, will improve both care and adherence.
- ▣ The continued use of existing antihypertensive medications, which are effective and well-tolerated.
- ▣ Expanding the use of free and fixed drug combinations, such as spironolactone and other mineralocorticoid receptor antagonists.
- ▣ Considering medications initially developed for heart failure and diabetes that also have blood pressure-lowering effects.

Liver as a Target for Preventing Diabetes

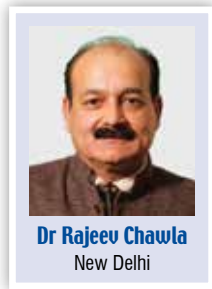


The liver is pivotal in glucose metabolism, managing blood sugar levels through glycogenesis and gluconeogenesis. It stores excess glucose as glycogen and releases it when necessary. Impaired liver function can disrupt glucose homeostasis and contribute to diabetes development. Research indicates that early detection and targeted treatment of nonalcoholic fatty liver disease (NAFLD) could help prevent T2D. Hence, liver-focused preventive strategies present a promising approach to tackling the diabetes epidemic.

Some effective pharmacological and non-pharmacological preventive measures include:

- ▣ Certain medications, such as GLP-1 agonists (e.g., liraglutide, semaglutide) and sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g., empagliflozin, canagliflozin), have demonstrated promising results in enhancing liver health and lowering diabetes risk.
- ▣ Ongoing clinical trials are exploring novel therapies, including farnesoid X receptor (FXR) agonists and apoptosis signal-regulating kinase 1 (ASK1) inhibitors, for treating NAFLD and preventing diabetes.
- ▣ Supplements like vitamin E and pioglitazone might also improve liver health and reduce diabetes risk, though further research is needed.
- ▣ Medications such as metformin and peroxisome proliferator-activated receptor (PPAR) agonists, especially PPAR-γ, show potential. These agents enhance insulin sensitivity and liver histology by reducing proinflammatory cytokines and increasing adiponectin production.
- ▣ A healthy diet, such as the Mediterranean diet, can help decrease liver fat and improve insulin sensitivity.
- ▣ Regular physical activity, including brisk walking or moderate-intensity exercise, reduces liver fat and enhances overall metabolic health.
- ▣ Maintaining or achieving a healthy weight is essential for improving insulin sensitivity and lowering the risk of NAFLD and T2D.

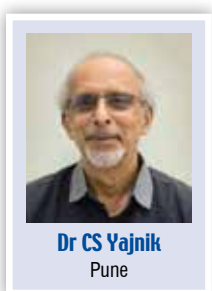
Metformin in Pregnancy: Haan ki Naa?



- Metformin remains the most effective drug for managing hyperglycemia in gestational diabetes mellitus (GDM), although its exact mechanisms are not fully understood.
- Metformin is a standard treatment option for pregnant patients with a history of T2D, GDM, or any degree of hyperglycemia detected during the second or third trimester.
- However, the blood glucose targets for pregnant women are very stringent (fasting blood sugar [FBS]: 90 mg/dL and postprandial blood sugar [PPBS]: 120 mg/dL). If metformin is insufficient for managing glucose levels, insulin may be initiated.
- According to guidelines, insulin is the primary treatment for any dysglycemia in pregnant women who do not achieve target glucose levels with medical nutrition therapy or lifestyle changes alone.
- Adding metformin can be beneficial for pregnant women with T2D on insulin who require higher doses.
- Additionally, metformin should be prescribed if insulin administration is problematic due to availability, cost, or the patient's inability to self-administer or self-monitor.
- The few contraindications to metformin include fetoplacental insufficiency, intrauterine growth restriction, hypertension, and pre-eclampsia. Patients with these conditions should be started on insulin immediately.
- In high-risk pregnancies, such as those involving macrosomia or small-for-gestational-age babies, insulin should not be delayed.
- For women with polycystic ovary syndrome, metformin is the safest drug for managing blood glucose levels. Although the ADA guidelines recommend discontinuing metformin after 12 weeks, studies have shown that continued use can prevent the progression from mild dysglycemia to GDM.
- Clinicians should advocate for early blood sugar testing (PPG >110 mg/dL) during pregnancy rather than waiting for the development of GDM in the second or third trimester before initiating treatment.

Overall, metformin is considered safe for use during pregnancy, and insulin should be added when metformin alone is insufficient for glycemic control. In 30% to 40% of clinical situations, patients may require insulin in addition to metformin to manage their blood glucose levels effectively.

Fetal Origin of Type 2 Diabetes



- The fetal origins of T2D emphasize the critical role of early life nutrition and development in determining long-term health outcomes.
- In Indian populations, research has shown that both undernutrition and overnutrition during gestation can increase the risk of T2D in later life.
- This phenomenon, often described as the “thrifty phenotype”, suggests that the fetus adapts to a limited supply of nutrients by developing insulin resistance and other metabolic changes.
- Although beneficial in the short-term, it predisposes the individual to diabetes and other chronic diseases in adulthood.
- The Pune Maternal Nutrition Study highlighted the significance of maternal nutrition before and during pregnancy in shaping the metabolic health of offspring.
- Children born to undernourished mothers were found to have lower birth weights and were more prone to developing central obesity and insulin resistance as they aged.
- Overall, early interventions aimed at improving maternal nutrition and fetal growth conditions are essential to break the cycle of diabetes transmission and reduce the burden of T2D in future generations.

Novel Non-Pharmacological Treatment of Diabetes: *Gryllus bimaculatus*

Gryllus bimaculatus, commonly known as two-spotted crickets, has emerged as a promising sustainable protein source. It is rich in essential amino acids and unsaturated fatty acids and offers significant benefits for managing diabetes and other health conditions. Clinical evidence has demonstrated the glucose-lowering effects of cricket powder through the AKT/mTOR pathway, providing a novel approach to diabetes management.



The “D&D” (Diabetes and Dietary) trial, which involved 1,000 patients using a dietary supplement derived from crickets, confirmed the therapeutic effects of this alternative protein in managing diabetes. In the trial, patients were classified into eight groups: Juvenile-T1DM (<17 years), Adult-T1DM (Originated from LADA and T2DM), LADA (latent autoimmune diabetes in adults), etc. Every 3 months, the patients were more than 20 different parameters such as HbA1c, microalbumin, fasting blood glucose, postprandial 2 hours, insulin resistance, HOMA-IR, LDL, HDL, etc.

Key findings include:

- HbA1c levels reduced from 12% to 6.5% within 3 months.
- Patients with T1D showed recovery in C-peptide levels and insulin secretion.
- Extremely high triglyceride levels (1,400 mg/dL) were normalized in 3 months.
- Improvement in diabetes-related complications, including:
 - Diabetic retinopathy
 - Peripheral neuropathy/numbness in the hands and feet
 - Nighttime urination reduced from 3 times to 1 time
 - Hyperglycemia/hypoglycemia
 - Hypertension
 - Hyperlipidemia
 - Erectile dysfunction, with increased testosterone levels
 - Hemiparalysis and obesity.

How to Prevent Fatty Liver in People with Diabetes and Prediabetes?

- The global prevalence of MASLD (metabolic-associated steatotic liver disease) in patients with T2D is approximately 65%.
- Fibrosis is the most significant prognostic factor in MASLD and is correlated with liver-related outcomes and mortality.
- Advanced fibrosis identifies patients requiring in-depth hepatological evaluation, including case-by-case confirmatory biopsy and intensive therapy.
- Primary care physicians, endocrinologists, gastroenterologists, and obesity specialists should screen for MASLD with advanced fibrosis using a four-step approach:
 - Step 1: Identify patients at risk.
 - Step 2: Conduct a thorough history and laboratory tests, including alcohol intake assessment, complete blood count (CBC), and liver function tests.
 - Step 3: Perform noninvasive testing for fibrosis.
 - Step 4: Measure liver stiffness.
- Approved and emerging pharmacotherapies for MASLD include resmetirom, pegozafermin, semaglutide, survodutide, tirzepatide, and others.

A case of a 64-year-old Latino man with a 14-year history of T2D was discussed. The patient presented with symptoms of hepatic steatosis on abdominal ultrasound.

- Based on the Fib-4 score and liver stiffness measurement, the patient was diagnosed with an intermediate risk for advanced hepatic fibrosis.
- The treatment plan included lifestyle modifications, initiation of GLP-1 receptor agonist-based therapy, and SGLT2 inhibitors, along with continued metformin and basal insulin (at a reduced dose).



Microbiota and the Prediction of Prediabetes and Type 2 Diabetes

The gut microbiome, composed of diverse bacteria, fungi, and other microorganisms, regulates digestion, immune function, and overall health. Recent research has highlighted its potential in predicting diabetes and prediabetes. Shifts in the microbiome composition, often influenced by diet and lifestyle, have been linked to metabolic diseases, including diabetes.

- Emerging research suggests that microbiome alterations may precede the onset of diabetes and prediabetes, offering a potential predictive tool. For example, a Finnish study identified bacterial changes during pregnancy that could predict postpartum prediabetes.
- Similarly, a German study recognized microbiome patterns that appeared before developing T2D. These findings suggest that microbiome profiling could aid in the early detection and prevention of diabetes.

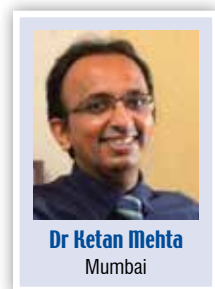
However, there are several challenges to overcome, such as:

- While some studies have linked microbiome changes to disease, few have successfully predicted disease onset.
- More large-scale research is needed to validate these findings, particularly in diverse populations like India.
- A multimodal approach incorporating clinical, biochemical, and lifestyle factors.
- Adding metabolomics to studies is crucial for improving prediction accuracy and translating microbiome insights into reliable clinical applications for diabetes management.



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Role of Beta-Blockers Across CV Continuum in Diabetes



- Sympathetic overdrive causes increased heart rate and contributes to multiple cardiovascular risk factors associated with hypertension (HTN).
- Indian patients with HTN are generally younger, have higher heart rates, and a greater prevalence of resistant HTN.
- Cardioselective and highly selective beta-1-blockers are essential for managing HTN effectively.
- Primary prevention:** Beta-blockers can be used to prevent cardiovascular events in individuals at risk, including those with diabetes and HTN.
- Secondary prevention:** Beta-blockers prevent the adverse effects of sympathetic overdrive and lower the risk of recurrent cardiovascular events and mortality in HTN patients.
- Heart failure management:** Beta-blockers are a cornerstone of HF treatment, improving symptoms and prolonging life expectancy.

Glucose/Weight/Vascular Protection: What should be my Priority?

Management of T2DM has become increasingly sophisticated, moving beyond traditional glucose-centric strategies towards a multifaceted approach that targets the broader cardio-renal-metabolic spectrum. Recent advances emphasize the integration of therapies that not only lower glucose but also confer protection against cardiovascular disease (CVD), HF, and CKD.

Modern guidelines now recommend agents such as SGLT2 inhibitors and GLP-1 receptor agonists for individuals with T2DM and comorbid atherosclerotic CVD, HF, or CKD. These medications have demonstrated efficacy in reducing MACE, hospitalizations for HF, and progression to end-stage kidney disease, independent of their glucose-lowering effects. This paradigm shift highlights the prioritization of vascular protection alongside glycemic control.

Additionally, weight management has emerged as a pivotal element in diabetes care. Advanced interventions, including the use of GLP-1 receptor agonists and dual incretin agonists like tirzepatide, offer substantial weight loss and metabolic improvements, with evidence supporting up to 15% body weight reduction. This level of weight loss is associated with significant reductions in HbA1c, blood pressure, and triglycerides, as well as improvements in NAFLD and other obesity-related complications.



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The Final Word: Idli Sambar or Misal Pav – Which is Better? Comparing FDCs in Diabetes Mellitus



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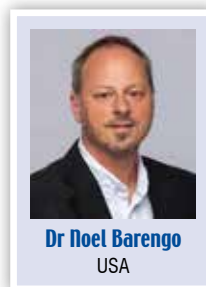
Dr. Shailaja Kale
Pune

Effective management of T2DM now demands a shift from traditional stepwise approaches to more sophisticated early intervention strategies. Emerging evidence emphasizes the need for combination therapies from the start of treatment, as they address the disease's complex pathophysiology beyond just reducing HbA1c levels. T2DM involves insulin resistance, beta-cell dysfunction, and abnormal glucose production, necessitating a comprehensive treatment approach.

Studies, including the VERIFY trial, show that early combination therapy—such as metformin and DPP-4 inhibitors—can significantly delay treatment failure, especially in patients with early-onset T2DM or those prone to rapid disease progression, like in South Asia. This approach helps maintain effective glycemic control and reduces the risk of complications like cardiovascular events and microvascular damage.

The “legacy effect” underscores the long-term benefits of early and aggressive glucose control, linking early stringent glycemic targets with reduced cardiovascular events and mortality years later. Fixed-dose combinations (FDCs) play a crucial role in this advanced strategy by combining agents with complementary actions, enhancing A1c reduction while minimizing risks like hypoglycemia and weight gain, and improving patient adherence.

How to Elaborate and/or Validate Risk Scores for Diabetes and Cardiovascular Complications?



Dr. Noel Barengo
USA

Two strategies can be used to identify a high-risk population for diabetes and hyperglycemia: a one-step strategy involving diagnostic tests such as oral glucose tolerance test, HbA1c, etc., or a two-step strategy. The two-step strategy includes using diabetes risk scores followed by diagnostic tests.

According to Wilson's criteria for screening, the condition should be an important health problem, and its natural history should be understood. There should be a recognizable latent or early symptomatic stage, and the screening test should be easy to perform, interpret, acceptable, accurate, and sensitive. Additionally, there should be an accepted treatment for the disease, which is more effective if started early. Policies should be established regarding who should be treated, focusing on cost-effective diagnosis and treatment, and case finding should be a continuous process.

The objective of developing FINDRISC was to create a simple, economical, and reliable tool that can be easily applied to the general population without requiring blood extraction.

Overall

- Validated screening tests exist.
- These screening tests have been successfully validated and implemented in various countries.
- Key challenges include monitoring attendance, determining short- and long-term benefits, implementing guidelines, and determining the appropriate time interval for screening tests.

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