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CONTENTS

HOW DO GLP1 AGONIST IMPACT CARDIOVASCULAR OUTCOMES?

Dr. Dina Mithani*

INTRODUCTION

Modern diabetes medications such as GLP-1 receptor agonists, have proven in many large studies to significantly reduce the incidence of serious heart problems and related issues, such as hospital visits for heart failure. In fact, scientific literature has shown some positive effects of GLP-1 agonists on heart health (1).

MECHANISM OF ACTION

GLP-1 agonists imitate the body's natural glucagon-like peptide-1 (GLP-1) hormone and activate GLP-1 receptors in the brain, pancreas and the gut. This helps lower blood sugar by boosting insulin secretion in response to glucose and suppressing glucagon release. In addition, they aid in weight loss by slowing down gastric emptying and curbing appetite, which results in reduced food intake. They help lower oxidative stress, prevent heart cells from dying and increase the use of glucose by the heart tissue. Together, these actions help protect the heart and improve its function.

GLP-1 agonists work in several ways: widen blood vessels, help the body get rid of salt, lower weight, improve cholesterol level, reduce inflammation, protect the kidney lower plaque buildup and change hormone pathways. Together, these actions help the heart function optimally. Studies show that these medications significantly lower the risk of heart-related issues, especially in patients with established heart disease (2).

SPECIAL FEARURES

The Incretin Effect

GLP-1 is an incretin hormone, meaning it stimulates the pancreas to secrete insulin in response to food intake, particularly glucose. Because it is glucose-dependent, this insulin secretion lowers the chance of hypoglycemia.

Prevents the release of glucagon

When glucose levels are high, GLP-1 prevents the pancreatic alpha cells from releasing glucagon, which lowers the amount of glucose produced by the liver (3).

Delays the emptying of the stomach

It helps regulate postprandial (after-meal) blood glucose spikes and encourages satiety by slowing the stomach's emptying (3).

Reduces Appetite & Promotes Satiety

GLP-1 works on the hypothalamus to decrease appetite, which aids in weight loss and is particularly advantageous for those who suffer from obesity and Type 2 diabetes mellitus (T2DM) (4).

Cardiovascular Benefits

Liraglutide and Semaglutide are two examples of GLP-1 receptor agonists that have demonstrated cardioprotective effects, which include lowering the risk of heart attack, stroke and cardiovascular death especially in high-risk individuals.

GLP-1 RAs influence nitric oxide (NO) and the renin-angiotensin-aldosterone system (RAAS) by increasing NO production, which contributes to vasodilation and counteract RAAS components by reducing Renin and Angiotensin II (ANG II) levels thus promoting natriuresis. This reduces blood pressure, decreases systemic vascular resistance and improves cardiovascular health (1).

β-Cell Protection

By preserving pancreatic function, GLP-1 may promote β-cell proliferation and survival

* Clinical fellow at Dr. *Chandalia's* Diabetes Endocrine Nutrition Management and Research Centre, Mumbai.
Email id: drnagodra@gmail.com

potentially slowing the progression of T2DM (2).

Short Half-life (Endogenous GLP-1)

Due to its quick degradation by the enzyme DPP-4 (dipeptidyl peptidase-4), natural GLP-1 has a very short half-life (1-2 minutes). As a result, GLP-1 receptor agonists and DPP-4 inhibitors had been created as therapeutic agents (5).

CURRENTLY AVAILABLE GLP1 AGONIST

Currently available GLP-1 agonists include semaglutide, liraglutide, dulaglutide, exenatide and lixisenatide along with the newer dual GIP/GLP-1 agonist, tirzepatide.

Semaglutide has been shown to improve heart health and overall body metabolism. This leads to better heart function and less thickening of the heart's left side and fluid buildup in the lungs. Using semaglutide also reduces heart stretching, inflammation and scarring, without changing the stiffness of heart cells (6).

Liraglutide provides substantial cardiovascular benefits for individuals with T2DM who are at high cardiovascular risk. It significantly reduces the incidence of major adverse cardiovascular events (MACE), including heart attack, stroke and cardiovascular-related death mainly due to lower rates of both cardiovascular and overall mortality. In addition, liraglutide helps lower the risk of microvascular complications, especially diabetic kidney disease. These protective effects are the result of multiple mechanisms, including better blood sugar control, weight loss, reduced blood pressure and anti-inflammatory actions (7).

By activating the GLP-1 receptor in pancreatic beta cells, dulaglutide raises intracellular cyclic AMP (cAMP) in beta cells, which triggers the release of insulin and lowers blood glucose levels. Additionally, dulaglutide decreases glucagon secretion and slows gastric emptying (8).

Exenatide is a human glucacon-like peptide-1(GLP-1) receptor agonist. By activating this receptor, insulin secretion is increased and glucagon secretion is decreased in a glucose dependant manner. Exenatide also reduces food intake and slows stomach emptying. These effects work synergistically to improve glycemic control by reducing the likelihood of hyper and hypoglycemia (9).

Adenylyl cyclase is activated when lixisenatide activates the GLP-1 receptor. This raises the cell's cyclic adenosine monophosphate concentration, which activates Epac1 and Epac2 as well as protein kinase A (PKA). When the triggering pathway is activated, PKA, Epac1 and Epac2 participate in the "amplification" pathway, which increases the release of insulin by releasing Ca2+ from the endoplasmic reticulum. Lixisenatide thus increases glucose-stimulated insulin secretion (10).

A synthetic polypeptide dual agonist for GLP-1 and GIP is called tirzepatide. "Twincretin" or tirzepatide, differs from GLP-1 receptor agonists in a number of ways . The drug is an analog of the gastric inhibitory polypeptide and is made up of 39 amino acids. In terms of function, tirzepatide lowers hyperglycemia and promotes the pancreas to release insulin. Furthermore, tirzepatide raises adiponectin levels. The dual agonism ability lowers the patient's appetite and lowers hyperglycemia considerably more than GLP-1 agonist drugs. Administering 5 to 15 mg of tirzepatide once a week to patients without diabetes to manage their obesity, had been shown to result in impressive weight loss with reductions ranging from 16.5% to 22.4% over a 72-week period. Tirzepatide showed more notable improvements in insulin sensitivity and β-cell function markers, according to post hoc analyses of fasting biomarkers (11).

CLINICAL TRIALS

Weight Loss

This small study examined the effectiveness of semaglutide across the baseline LVEF strata in patients with the obesity phenotype of heart failure (HF) with preserved ejection fraction (HFpEF) in the STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and HFpEF) trial.

Semaglutide 2.4 mg once weekly was given in this trial. Comparing the semaglutide group

to the placebo group in this trial, revealed a significant difference in the 6-minute walk distance, improved heart failure symptoms and more substantial weight loss. The STEP-HFpEF trial is significant since it shows the benefits of semaglutide for non-diabetic people with obesity and HFpEF. The continuing STEP-HFpEF DM trial is now investigating the effects of weekly injections of 2.4 mg semaglutide in patients with obesity, HFpEF and T2DM (12).

Oral semaglutide's dose-dependent impact was assessed and proven in the Japanese PIONEER 9 research. Compared to a placebo and 0.9 mg of liraglutide, a higher dosage of oral semaglutide produced a greater decrease in HbA1c and induced weight loss. Increases in dulaglutide dosage from 1.5 mg to 3 mg or 4.5 mg dose had comparable effects; the safety profile was comparable whereas the weight and HbA1c reductions were dose-related (13).

Despite previous evidence from the Look AHEAD trial suggesting a limited efficacy of modest body weight loss on cardiovascular risk reduction in diabetic patients, a post hoc reanalysis found that individuals who lost more than 10% of their body weight may stand at a lower risk for future cardiovascular outcomes. Notably, those with diabetes lose less weight than those without; both groups can lose up to 10% to 20% of their body weight with higher permitted dosages of tirzepatide and semaglutide. The ongoing STEP and SURPASS-CVOT trials may help determine the extent to which weight loss contributes to cardiovascular benefits (14).

Inflammation

One of the main risk factors for heart disease is mild inflammation. Treatment with tirzepatide has been shown in clinical trials to have a favorable effect on inflammatory markers. Tirzepatide treatment decreased the levels of specific biomarkers associated with inflammation and endothelial dysfunction linked to cardiovascular events in a dose-dependent manner in a 26-week phase 2 trial involving obese patients with T2DM, suggesting an overall improvement in the cardiovascular risk profile. To ascertain the additional effects of tirzepatide on cardiovascular risk factors, biomarkers for inflammation, endothelial dysfunction and cellular stress were evaluated at baseline as well as at 4, 12 and 26 weeks in this post hoc investigation. After 26 weeks, YKL-40 (also known as chitinase-3 like-protein-1), intercellular adhesion molecule 1 (ICAM-1), leptin and growth differentiation factor 15 levels were lower after therapy with tirzepatide at 10 and 15 mg than baseline. In addition, tirzepatide treatment reduced leptin and YKL-40 levels in comparison to dulaglutide and placebo. When compared to both placebo and dulaglutide, treatment with a 15 mg dose of tirzepatide decreased ICAM-1 levels. It also decreased high-sensitivity C-reactive protein levels compared to baseline and placebo, but not to dulaglutide.

Although the precise method by which tirzepatide reduces these inflammatory indicators is unclear, it may be related to the compound's dual agonist characteristics. Both GLP-1 and GIP have anti-inflammatory qualities and when these two hormones are combined in tirzepatide, inflammation may be reduced more dramatically than when each hormone is used alone (15).

Cardiovascular Benefits

An important accomplishment was the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) experiment, which showed the benefits of liraglutide for the cardiovascular system in people with T2DM and high cardiovascular risk. Participants included more than 9,000 patients across a 3.8-year follow-up period. The results showed that liraglutide reduced the risk of MACE (the main endpoint, which included cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke) by 13% in high-risk adults with T2DM (16).

The cardiovascular benefits of weekly injected GLP-1 receptor agonists have been shown in the Harmony outcomes trials, REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) and SUSTAIN-6 (trial to evaluate cardiovascular and other long-

term outcomes with semaglutide in subjects with T2DM). Semaglutide reduced the incidence of MACE in T2DM patients by 26% in the SUSTAIN-6 study, mostly by lowering the nonfatal stroke rate (39%) when compared to a placebo (1).

While the SUSTAIN-6 and REWIND studies examined GLP-1 RA in diabetics with different cardiovascular risk profiles, the Harmony Outcomes study included patients with T2DM and pre-existing atherosclerotic cardiovascular disease (ASCVD). When compared to a placebo, albiglutide significantly reduced MACE in those high-risk patients; this difference was most pronounced in lowering the rate of myocardial infarction, as opposed to semaglutide in the SUSTAIN-6 study. GLP-1 receptor agonists have been shown by numerous CVOTs to reduce MACE in T2DM patients in comparison to a placebo (17).

In the REWIND research, dulaglutide also reduced the risk of non-fatal strokes when compared to a placebo, yielding similar results. In both trials, participants treated with GLP-1 RA and those given a placebo had comparable rates of cardiovascular death and nonfatal myocardial infarction. The Harmony Outcomes research concentrated on individuals with T2DM and proven ASCVD, even though the SUSTAIN-6 and REWIND studies examined GLP-1 RA in diabetics with a variety of cardiovascular risk factors. Albiglutide significantly reduced MACE in those high-risk people when compared to a placebo. In the SUSTAIN-6 study, this difference was especially noticeable when compared to semaglutide in terms of lowering the incidence of myocardial infarction. In the AMPLITUDE-O trial, effeglenatide, another weekly injection of a GLP-1 receptor agonist, was evaluated (18).

In the ELIXA and EXSCEL studies, GLP-1RAs (daily lixisenatide and weekly exenatide, respectively) did not show an advantage in MACE reduction versus placebo, but demonstrated non-inferiority to placebo for the primary composite outcome of MACE. The ELIXA trial encompassed patients who experienced a recent cardiovascular event (those with acute coronary syndrome within 180 days prior to randomization) and while there was no observed benefit in reducing MACE among patients treated with lixisenatide compared to placebo, the findings demonstrated the cardiovascular safety of lixisenatide in this particular high-risk group. A novel oral form of the GLP-1 receptor agonist was assessed in the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 study. Although it did not show superiority in lowering MACE, the 2019 release provided significant evidence regarding the safety and oral administration of GLP-1 receptor agonists, expanding the range of therapeutic options available to people with T2DM. The SOUL (Semaglutide cardiovascular outcomes) experiment is now investigating the cardiovascular benefits of oral semaglutide in T2DM patients with proven atherosclerotic cardiovascular illnesses and/or chronic renal disease. GLP-1 receptor agonists have been shown to reduce MACE and improve chronic kidney disease in individuals with T2DM, according to a meta-analysis of these eight CVOTs that included 60,080 patients (19).

A possible dose-dependent effect on the incidence of MACE was seen in AMPLITUDE-O. In comparison to a placebo, the estimated hazard ratio for a 6 mg weekly dose of efpeglenatide was 0.65 (95% CI, 0.5 to 0.86) and for a 4 mg weekly dose, it was 0.82 (95% CI, 0.63 to 1.06). Patients receiving 0.5 mg and 1 mg of semaglutide weekly in the SUSTAIN-6 study showed similar effects on glycemic control, hypoglycemia rates and MACE risk reduction. Particularly for individuals with established atherosclerotic cardiovascular disease, data from cardiovascular outcome studies shown a significant and steady decline in atherothrombotic events (20).

There were 83,258 participants in 13 CVOTs overall. MACE (OR 0.86, 95% CI: 0.80 to 0.94, $p < 0.01$), overall mortality (OR 0.87, 95% CI: 0.82 to 0.93, $p < 0.001$), cardiovascular mortality (OR 0.87, 95% CI: 0.81 to 0.94, $p < 0.001$), stroke (fatal: OR 0.74, 95% CI: 0.56 to 0.96, p =

0.03; non-fatal: OR 0.87, 95% CI: 0.79 to 0.96, p = 0.005), coronary revascularization (OR 0.86, 95% CI: 0.74 to 0.99, p = 0.023) and composite kidney outcomes (OR 0.76, 95% CI: 0.67 to 0.85, p < 0.001) were all significantly reduced by GLP-1RAs. MACE was significantly reduced with GLP-1RA in both sexes. Furthermore, GLP-1RA reduced MACE regardless of eGFR level, BMI, or history of CVD.

569 out of 8803 patients (6.5%) in the semaglutide group and 701 out of 8801 patients (8.0%) in the placebo group experienced a primary cardiovascular end-point incident (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001) (17).

Semaglutide treatment improved outcomes for both heart failure with reduced ejection fraction groups (HR 0·65, 95% CI 0·49–0·87 for MACE; 0·79, 0·58–1·08 for the composite heart failure endpoint) and heart failure with preserved ejection fraction groups (0·69, 0·51–0·91 for MACE; 0·75, 0·52–1·07 for the composite heart failure endpoint). However, the absolute event rates were higher for those with reduced ejection fraction than the later. Benefits for MACE and the heart failure composite did not significantly change according to baseline age, sex, BMI, New York Heart Association status, or diuretic use. Regardless of the type of heart failure, semaglutide caused fewer severe adverse events than a placebo (21).

Regardless of whether tirzepatide was used as an adjuvant therapy or as a stand-alone treatment, patients who received it showed significantly lower systolic and diastolic blood pressure than the control group. In conclusion, the administration of tirzepatide resulted in a 4.8 mmHg drop in systolic blood pressure and a 1.7 mmHg drop in diastolic blood pressure. In Japanese patients with T2DM, tirzepatide appears to have a stronger impact on blood pressure. When compared to baseline data, tirzepatide reduced systolic blood pressure by 11.0 mmHg and diastolic blood pressure by 5.6 mmHg at a dosage of 15 mg. To determine the precise aspects of tirzepatide treatment that led to the higher blood pressure reduction observed in Asian populations, more research is required. The SURMOUNT-1 ABPM sub-study evaluated the effects of tirzepatide on the 24-hour average systolic blood pressure, diastolic blood pressureand heart rate (HR) measured during 24-hour ambulatory blood pressure monitoring (ABPM) in obese people without T2DM. Tirzepatide demonstrated statistically significant and clinically meaningful reductions in the mean 24-hour systolic blood pressure at all doses and decreased diastolic blood pressure at the two lower dosages after 36 weeks of treatment (22).

A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants with T2DM (SURPASS-CVOT) is a continuous cardiovascular outcome trial that aims to evaluate the potential benefits of dual GIP and GLP-1 receptor agonist, which has shown better glucose-lowering and weight-loss effects than GLP-1 receptor agonist alone. There were 13,299 T2DM patients with either established cardiovascular disease or a high risk of developing cardiovascular disease in this randomized, double-blind, controlled trial with an active comparator. For a maximum of 236 weeks, patients were randomized to receive either tirzepatide or dulaglutide once weekly. The study's primary outcome measure is a composite of MACEs, which includes non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. A more comprehensive assessment of deaths from cardiovascular problems, myocardial infarction, stroke, coronary revascularization, admissions for unstable angina, or heart failure comprise secondary outcome indicators. Secondary outcomes also include changes from baseline in body mass, urine albumin to creatinine ratio, lipid profiles and HbA1c values.

The forthcoming cardiovascular outcome trial SURPASS-CVOT (NCT04255433) will assess the clinical significance of the aforementioned cardiovascular risk factor changes brought on by tirzepatide; however, a pre-specified cardiovascular meta-analysis found that tirzepatide did not increase the risk of MACEs in people with Type 2 diabetes in comparison to controls. All seven randomized controlled

studies with a duration of at least 26 weeks that were a part of the tirzepatide T2DM clinical development program, SURPASS, were included in this pre-specified meta-analysis. Comparing the duration between the combined tirzepatide and control groups for the first confirmed occurrence of 4-component MACEs (MACE-4) that is, cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina was the main goal of this meta-analysis. Tirzepatide's hazard ratios compared to controls were 0.80 (95% CI), 0.57–1.11) for MACE-4, 0.90 (95% CI, 0.50–1.61) for cardiovascular death and 0.80 (95% CI, 0.51–1.25) for all-cause mortality (23).

In SURPASS-4, a trial involving patients with known coronary, peripheral arterial or cerebrovascular disorders, or those at high risk for these problems, the effect of tirzepatide on cardiovascular events was investigated. No tirzepatide dosage in this study significantly increased the risk of cardiovascular events. In contrast, the risk of any MACE (myocardial infarction, stroke, angina hospitalization, or all-cause death) was calculated to be 0.50 (95% CI, 0.26–0.95) for patients on the highest tirzepatide dosage (15 mg weekly). However, only 11 incidents in the tirzepatide 15 mg weekly sample (and 62 events with insulin glargine treatment) supported this conclusion. Overall, when compared to controls, tirzepatide did not increase the likelihood of MACEs in T2DM subjects. The aforementioned tripeptide-based long-term cardiovascular outcome trials will provide conclusive evidence on tirzepatide's ability to protect patients with T2DM who are at high cardiovascular risk from recurrent cardiovascular events (24).

CONCLUSION

GLP-1 receptor agonists are highly effective and have become a breakthrough therapy for T2DM and obesity offering multiple benefits. Although they have many benefits, using them is also linked to risks, including a high incidence of gastrointestinal side effects like nausea and vomiting as well as a possible risk of pancreatitis. These medications' safety profile and long-term effects are still being studied, and more research is required to resolve these concerns. Overall, the beneficial effects of GLP-1 RA on cardiovascular outcomes in high-risk T2DM patients are probably due to a combination of metabolic, vascular, antithrombotic and anti-inflammatory actions.

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CHALLENGES IN PATIENTS WITH YOUTH-ONSET DIABETES WITH RESPECT TO ADHERENCE

Rishi Shukla*, Sandeep D Paimode**

INTRODUCTION

Adolescence represents a pivotal period of human development, encompassing individuals aged 10 to 19 years, as delineated by the World Health Organization (WHO). The broader category of "young people" extends this range up to 24 years. This transitional stage is marked by profound physical, psychological and social transformations that significantly influence long-term health behaviours and outcomes. The onset of a chronic illness such as diabetes during this already dynamic period introduces substantial medical and psychosocial complexities.

Diabetes is a chronic metabolic condition characterized by persistent hyperglycemia, resulting from impaired insulin secretion, diminished insulin action, or a combination of both. Among its variants, Type 1 Diabetes Mellitus (T1DM) is predominantly diagnosed in children and adolescents. This autoimmune disorder arises when the body's immune system erroneously targets and destroys the insulin-producing beta cells of the pancreas, culminating into absolute insulin deficiency, thus necessitating lifelong insulin therapy.

The pathogenesis of T1DM is multifactorial, involving an interplay of genetic susceptibility, environmental exposures such as viral infections and dietary factors and dysregulated immune responses. Alarmingly, the global incidence of T1DM continues to escalate at an estimated annual rate of 3%, a trend likely attributable to shifting environmental and lifestyle patterns, including the rising prevalence of childhood obesity, sedentary lifestyle patterns and suboptimal infant feeding practices (1).

Managing diabetes in the youth population presents a distinct set of challenges, necessitating a comprehensive, multidisciplinary approach. Effective management must address a spectrum of factors, including psychological stress, hormonal and physiological fluctuations, evolving family dynamics, complex therapeutic regimens, socio-economic constraints and the critical transition from pediatric to adult care systems. Poor adherence to treatment remains a prevalent issue, often resulting in deteriorating glycemic control and heightened risk of acute and chronic complications. Accordingly, early identification and proactive mitigation of these barriers are essential to enhancing long-term health outcomes for young individuals living with diabetes.

PSYCHOLOGICAL FACTORS

Emotional Burden and Mental Health

For many adolescents, living with diabetes is not just a physical challenge; it is an emotional journey filled with uncertainty, frustration and isolation. The constant demands of managing their condition like checking blood sugar levels multiple times a day, administering insulin injections, planning every meal and staying vigilant against the risk of dangerous lows (hypoglycemia) can feel overwhelming. Unlike their peers, they do not have the luxury of spontaneity; every decision, from grabbing a snack to playing sports, requires careful thought and monitoring.

This continuous pressure can take a significant toll on their mental health. Feelings of stress, anxiety and even depression are common. Many

* Senior Director & Head; Department of Endocrinology, Regency Healthcare Founder, Center for Diabetes & Endocrine Diseases, Kanpur.
Email id: drrishishukla@gmail.com

** IAP Advance and Basic NRP Instructor, IAP BLS Instructor, Fellow Pediatric Endocrinology, CDER Regency Hospital, Kanpur.

teenagers struggle with a sense of being different, often hiding their condition to avoid judgment or pity. Some withdraw socially, fearing they won't be understood or accepted. The emotional weight of being 'the one with diabetes' can be heavy especially in a world where fitting in matters so much.

To make matters worse, the stigma around chronic illnesses can deepen these emotional wounds. Misunderstandings, insensitive comments, or lack of support from peers and even adults can reinforce the belief that they are alone in their struggle. Over time, this may erode their confidence and motivation, leading to poor adherence to treatment and serious consequences for their long-term health.

That is why emotional support must be considered just as vital as medical treatment. These young individuals need to feel seen, heard and understood not just by doctors, but by their families, schools and communities. Open conversations, peer support groups, mental health counselling and empathy from caregivers can make a world of difference. When we take the time to truly understand what they are going through, we do not just improve adherence, we help them reclaim their confidence and quality of life. Personalized interviews can help identify stressors and anxiety, allowing for a tailored treatment plan (1). A tailor-made approach is the way forward to effectively address the unique needs and challenges faced by adolescents.

Impact on Adherence

There is a strong and deeply concerning connection between poor mental health and poor adherence to diabetes management. When adolescents experience emotional distress whether it be anxiety, depression, or low self-esteem, it can significantly reduce their motivation and ability to stick to complex treatment routines. The emotional burden can become so overwhelming that checking blood sugar, administering insulin, or even attending medical appointments may feel like insurmountable tasks.

For some teenagers, this psychological strain may lead to dangerous coping mechanisms. One alarming example is the intentional omission of insulin doses as a method of weight control, a disordered behavior commonly referred to as "diabulimia." This condition is particularly insidious because it combines the physical risks of uncontrolled diabetes with the psychological harm of an eating disorder. Adolescents engaging in this behaviour may experience rapid weight loss in the short term, but the long-term consequences can be severe, including diabetic ketoacidosis, end-organ damage and even death.

What makes these situations even more challenging is that such behaviours are often hidden. Teens may not speak openly about their mental health struggles or the reasons behind their non-adherence, leaving caregivers and healthcare providers unaware of the true depth and extent of gravity of their distress.

This highlights an urgent need for a more holistic approach to diabetes care, one that places equal emphasis on mental health. Routine psychological screenings, open and nonjudgmental communication and access to mental health professionals should be standard components of diabetes management. When adolescents are supported emotionally, they are far more likely to engage positively with their care, avoid risky behaviours and take ownership of their health. In short, addressing mental well-being is not optional, it's a vital part of saving lives.

Strategies for Support

To mitigate these challenges, comprehensive diabetes education programs should be introduced early and tailored to the cognitive level of the adolescent. These programs should not only focus on medical management but also address emotional coping skills and stress reduction techniques. Peer support groups, whether online or in person, offer a safe space for sharing experiences and receiving emotional support. Periodic diabetes camps can be effective in creating a community for youth, helping them understand that they are not alone in their journey.

Personalized counselling sessions involving mental health professionals can also help identify and address underlying emotional and psychological challenges. Regular mental health screenings should be integrated into routine diabetes care to ensure timely intervention.

PHYSIOLOGICAL CHANGES DURING ADOLESCENCE

Puberty and Insulin Resistance

Puberty is characterized by hormonal fluctuations, particularly increased levels of growth hormone and sex steroids. These changes contribute to increased insulin resistance, even in healthy adolescents. For those with T1DM, this physiological insulin resistance can make glycaemic control particularly challenging during this phase. Adolescents often require higher insulin doses during puberty to maintain target blood glucose levels.

Glycaemic Variability

The interplay between hormonal surges, growth spurts, irregular meal patterns and variable physical activity levels results in erratic blood glucose levels. These fluctuations not only increase the risk of both hyperglycemia and hypoglycemia but also add to the emotional stress of diabetes management.

Clinical Management

During adolescence, clinicians must maintain vigilant surveillance of glycaemic control due to the complex interplay of pubertal hormonal fluctuations, increased insulin resistance and rapid somatic growth. This period is often marked by heightened variability in blood glucose levels, necessitating frequent reassessment and titration of insulin regimens to match the evolving physiological demands. Both basal and bolus insulin requirements may increase significantly and adjustments should be made based on comprehensive glucose profiling.

The integration of advanced technologies such as Continuous Glucose Monitoring (CGM) systems offers a valuable tool in this context. CGMs provide real-time data on interstitial glucose levels, revealing patterns of hyperglycemia, nocturnal hypoglycemia and glycaemic excursions that may not be detected through traditional self-monitoring of blood glucose (SMBG). By analysing time-in-range (TIR), glycaemic variability and sensor glucose metrics, healthcare providers can make informed and timely modifications to insulin dosing, thereby optimizing metabolic control.

In parallel, individualized medical nutrition therapy (MNT) should be emphasized. Dietitians specializing in paediatric and adolescent endocrinology play a crucial role in educating patients and families on macronutrient distribution, carbohydrate counting and glycaemic index management. Nutritional plans must strike a balance between supporting linear growth, pubertal development and maintaining euglycemia. Regular assessment of dietary intake, physical activity and insulin-to-carbohydrate ratio is essential to ensure synergy between insulin therapy and nutritional strategies. It is essential to adjust insulin or medication doses during puberty and maintain good glycaemic control (1).

Ultimately, a proactive, multidisciplinary approach involving endocrinologists, diabetes educators, dietitians and mental health professionals is vital to managing the dynamic physiological changes of adolescence and minimizing the risk of both acute and long-term diabetes-related complications.

PARENTAL INVOLVEMENT AND FAMILY DYNAMICS

Balancing Supervision and Autonomy

Adolescence is a time when young individuals seek independence and begin to assert autonomy over their daily lives. For youth with diabetes, this developmental milestone can be complicated. Parents may struggle between allowing independence and ensuring adequate supervision to prevent treatment lapses.

Overbearing parental behaviour can lead to rebellion or resentment in the adolescent, resulting in poor adherence. On the other hand,

complete parental disengagement may leave the adolescent unequipped to handle their condition independently.

Effective Parenting Strategies

The goal should be a gradual transfer of responsibility from parent to child, with ongoing guidance. Parents should remain involved in the overall management of diabetes, such as helping to interpret blood glucose trends and attending clinic visits, while encouraging adolescents to take charge of daily tasks like insulin administration and meal planning. However, complete parental disengagement can negatively impact adherence and glycaemic control (2).

Family therapy sessions and parenting workshops can be beneficial in helping families navigate this transition. Communication within the family should be open, supportive and non-judgmental to foster trust and cooperation.

COMPLEXITY OF TREATMENT REGIMENS

Daily Management Demands

Managing T1DM involves multiple daily insulin injections or use of an insulin pump, frequent blood glucose monitoring (often six to eight times a day), carbohydrate counting, managing physical activity and preparing for sick days. This demanding regimen can be overwhelming, particularly for adolescents who already juggle academic, social and extracurricular commitments.

Technological Aids and Innovations

Technological advancements have made diabetes management more user-friendly. Mobile applications that help with carb counting, insulin dose calculations and symptom tracking have become valuable tools for youth. Continuous Glucose Monitors (CGMs) provide real-time glucose readings, reducing the need for frequent finger-pricks and improving glycaemic control.

Insulin pumps, especially those integrated with CGM systems, allow for more flexible insulin delivery and better glucose control. However, access to these technologies can be limited by cost and availability, especially in resource-limited settings.

Individualized Care

Each adolescent is unique in their medical, emotional and social needs. Treatment plans should be individualized and regularly updated based on the patient's lifestyle, preferences and glycaemic targets. A multidisciplinary approach involving endocrinologists, dietitians, psychologists and diabetes educators is ideal for comprehensive care. Where feasible, Continuous Glucose Monitoring (CGM) and insulin pumps should be offered. Individualized treatment plan should be offered to each patient (3).

SOCIO-ECONOMIC STATUS AND ACCESS TO CARE

Financial Barriers

In low- and middle-income countries, the high cost of insulin, glucometers, testing strips and clinic visits can create substantial financial burdens. Families with limited resources may struggle to afford necessary supplies, leading to irregular insulin use and poor glycaemic control. In such situations, alternative therapies or indigenous remedies may be pursued, which are not scientifically validated and can delay proper treatment. Due to the cost of treatment and lack of knowledge about the disease, they often consider alternative or indigenous remedies for the treatment of diabetes (4).

Educational Disparities

Lack of awareness about diabetes and its management is another major barrier. In communities with low literacy levels, myths and misconceptions about diabetes persist, contributing to stigma and delay in seeking care.

Support Programs and Policy Initiatives

Programs like the Changing Diabetes in Children (CDiC) initiative aim to bridge these gaps. CDiC provides free or subsidized insulin, glucometer strips and diabetes education to underprivileged children. Collaborations with government health departments and non-governmental organizations are crucial to expand access to care.It is working

with central and state governments to provide subsidised or free insulin and glucometer strips (5).

Policymakers should prioritize health equity by ensuring that life-saving diabetes supplies are covered under national health insurance schemes and public health programs. Mobile health clinics and telemedicine can also be used to reach remote and underserved populations.

TRANSITION FROM PAEDIATRIC TO ADULT DIABETES CARE

The Transitional Gap

One of the most vulnerable periods for youth with diabetes is the transition from paediatric to adult diabetes care. During this time, young adults often face challenges such as loss of a familiar care team, difficulty scheduling adult clinic appointments and anxiety about managing their condition independently. Studies have shown that glycaemic control often worsens during this transition period.

Bridging the Gap

The transition from paediatric to adult diabetes care represents a pivotal, yet frequently overlooked phase in the continuum of diabetes management. This shift often coincides with other life transitions such as leaving home, starting college or employment and gaining independence which can compound the challenges associated with managing a chronic illness. For many young adults, this handover can feel abrupt, disorienting and emotionally unsettling. They may struggle to identify an adult endocrinologist who aligns with their needs, face long wait times for appointments, or experience apprehension in building rapport with unfamiliar healthcare providers.

Alarmingly, there may be a significant lapse in medical follow-up during this transition period often spanning several months placing the patient at risk of lapses in treatment, poor glycaemic control and loss to follow-up. This is particularly concerning in individuals with T1DM Mellitus, where uninterrupted care is critical to avoid acute complications such as diabetic ketoacidosis (DKA) and to maintain long-term metabolic stability.

To mitigate these risks, a structured and proactive transition process must be implemented. Paediatric diabetes teams should begin preparing adolescents for adult care well before the anticipated transition, ideally starting in mid-adolescence. This includes gradually increasing the young person's involvement in self-management, providing education on navigating adult healthcare systems and fostering decision-making autonomy.

A formal written transition summary should be provided to both the patient and the receiving adult care team. This document should include the patient's full medical history, insulin regimen details, most recent glycaemic metrics (HbA1c, CGM data, etc.), screening results for complications, psychosocial assessments and any challenges in adherence or mental health concerns.

Whenever feasible, a period of overlapping care involving both paediatric and adult teams is strongly recommended. Joint consultations either in person or via telemedicine can facilitate a smoother handover, reduce patient anxiety and foster continuity of care (2). Such collaborative models not only improve health outcomes but also empower young adults to engage more confidently in their own care.

Ultimately, the success of this transition depends on a multidisciplinary, patient-centered approach that recognizes the emotional, developmental and clinical complexities of this vulnerable period. Investing in structured transition protocols is not just good practice, it is essential for safeguarding the long-term health and well-being of youth with diabetes.

THE ROLE OF SCHOOLS AND COMMUNITIES

School-Based Interventions

Schools play a vital role in the daily lives of adolescents and must be equipped to support students with diabetes. Teachers, school nurses and administrators should receive training on

diabetes management, recognizing signs of hypoglycemia and hyperglycemia and responding to emergencies.

Creating a supportive and inclusive environment helps students manage their condition without fear of judgment or stigma. School policies should allow flexibility in meal timing, testing glucose levels and administering insulin.

Community Involvement

Community-based programs play a pivotal role in complementing clinical care by fostering awareness, reducing stigma and facilitating peer-led support networks for youth with diabetes. These initiatives serve as critical extensions of the healthcare system, particularly in resource-limited settings where access to specialized endocrinology services may be limited.

Strategically designed public health campaigns rooted in evidence-based messaging—can educate communities about the early signs and symptoms of youth-onset diabetes, such as polyuria, polydipsia, unexplained weight loss, fatigue and recurrent infections. By promoting early recognition, these efforts contribute to timely diagnosis and initiation of treatment, thereby reducing the risk of acute presentations like DKA, which is still a common initial presentation in undiagnosed youth.

Moreover, community outreach programs can play a transformative role in dispelling persistent myths and misconceptions surrounding diabetes. Many adolescents and families still attribute the disease to contagion, curses, or poor lifestyle choices alone; misunderstandings that can delay care or lead to harmful alternative treatments. Culturally sensitive education, delivered through schools, local health workers and faith-based organizations, can counter these false narratives and replace them with accurate, actionable knowledge.

Peer support groups, diabetes camps and mentorship initiatives offer adolescents a safe space to share experiences, learn practical self-management skills and build resilience. These programs have been shown to improve treatment adherence, enhance psychosocial well-being and reduce diabetes-related distress. Involving trained peer educators or youth advocates with lived experience of managing diabetes can significantly enhance the relatability and effectiveness of these interventions.

Ultimately, integrating community-based programs with formal healthcare services promotes a more holistic, inclusive model of care; one that not only treats the disease but nurtures the individual behind the diagnosis. A well-informed, supportive community can serve as both a safety net and a catalyst for empowering youth with diabetes to lead healthier, more confident lives.

CONCLUSION

Youth-onset diabetes is a multifaceted condition that requires more than just medical intervention. The challenges faced by adolescents with diabetes span physical, emotional, social and economic domains. Effective management calls for a coordinated, empathetic and individualized approach involving healthcare providers, families, schools, policy makers and communities.

By addressing psychological stressors, adjusting for physiological changes, involving families appropriately, simplifying treatment regimens, supporting financially disadvantaged populations and ensuring seamless healthcare transitions, we can significantly improve the quality of life and long-term health outcomes for young individuals living with diabetes.

LET'S STAND TOGETHER

Youth living with diabetes deserve more than just treatment, they require unwavering, compassionate and coordinated care that addresses not only their medical needs but also their emotional, social and developmental challenges. Their journey is complex, marked by fluctuating glycaemic patterns, evolving self-identity and the pressures of adolescence, all of which demand a sensitive, multidisciplinary approach.

As healthcare professionals, caregivers, educators and community stakeholders, it is our collective responsibility to ensure that no young person faces this condition alone. Through early diagnosis, evidence-based interventions, robust psychosocial support and seamless care transitions, we can empower them to achieve optimal glycaemic control while preserving their quality of life and emotional well-being.

Let us commit to creating a healthcare ecosystem where young individuals with diabetes are not only treated but truly understood, supported and equipped to thrive. Together, through shared effort and sustained advocacy, we can help them live not just longer but healthier, fuller and more confident lives.

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EARLY DETECTION OF CORONARY ARTERY DISEASE (CAD) IN PEOPLE WITH DIABETES:

EVIDENCE, PRACTICE AND FUTURE DIRECTIONS

Debasis Basu*, Dilip Kumar, Soubhik Sinhababu***, Surajeet Kumar Patra****, Soutri Ghosh*****

INTRODUCTION

Coronary Artery Disease (CAD) is central to the excess cardiovascular (CV) risk in people with diabetes mellitus. Epidemiological, pathophysiological and clinical trial data universally confirm the substantial increase in risk among diabetic populations, an effect compounded by the high prevalence of silent disease (1-5). Compared to non-diabetics, people with Type 2 Diabetes Mellitus (T2DM) have at least an equal, if not higher, risk of fatal cardiovascular events versus those with known CAD but no diabetes (1,2,3,4,23,43). In Type 1 Diabetes Mellitus (T1DM), cardiovascular disease quickly becomes the leading cause of mortality after only 10 years of disease (3,45).

Silent myocardial ischemia (SMI) and unrecognized myocardial infarction (MI) affect a large proportion between 11–60% of diabetics in various cohorts, reflecting diabetic neuropathy, endothelial dysfunction and altered pain perception (6,9,12,32). This "silent" nature makes effective screening and timely intervention critical. However, the clinical benefit, cost-effectiveness and most appropriate approach to CAD screening in asymptomatic diabetics.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF CAD IN DIABETES

Figure 1 shows numerous meta-analyses and longitudinal cohorts have mapped the elevated CAD risk landscape in diabetes. Individuals with T2DM face a two-to-four-fold increased risk of CAD related mortality (1,4,23). For those with T1DM, cardiovascular disease (CVD) accounts for approximately 40% of deaths after 20 years of disease duration (3,45). Additionally, silent CAD is notably prevalent, occurring in up to 60% of high-risk diabetic patients, often being discovered incidentally during evaluations for other conditions (6,9,12,32,46,47,48).

KEY MECHANISMS

The mechanism contributing to cardiovascular complications in diabetes include endothelial dysfunction, a process that affects both microvascular and macrovascular systems and begins early, even before the onset of hyperglycemia (10,29). A prothrombotic state is also commonly observed, characterized by altered coagulation, reduced nitric oxide (NO) availability and increased platelet activation (6,10,29). Additionally, diabetic neuropathy; both autonomic and sensory plays a critical role which blunts chest pain and contribute to the development of asymptomatic (silent) ischemia (6,12,28).

* Founder, Healious Global Pvt Ltd., Kolkata.
Email Id: drbasu.metta@gmail.com

** Director Cath Lab, Manipal Hospital Bypass, Kolkata.

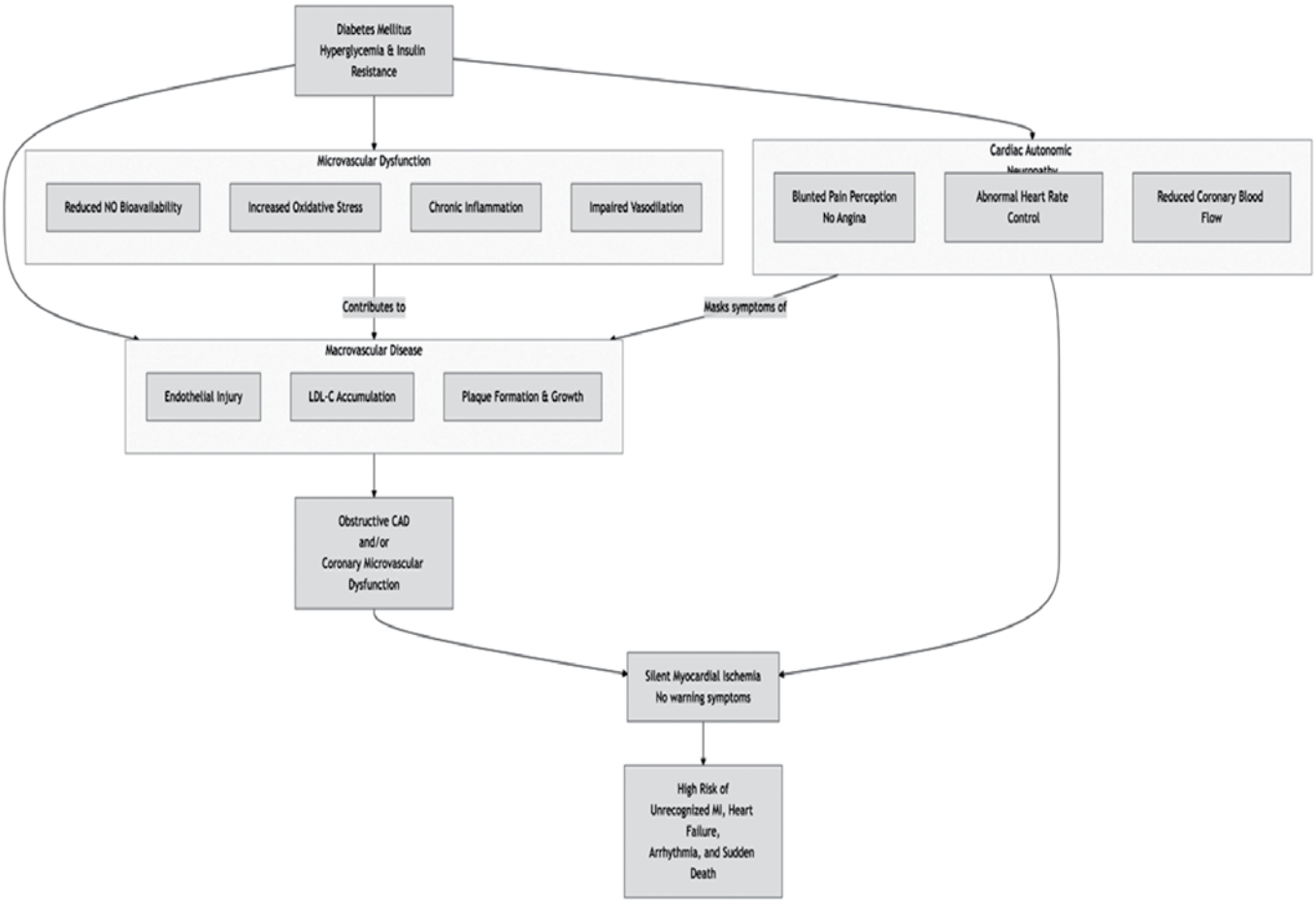
*** Medical Officer, Amjhuri RH Hirbandh, Bankura, West Bengal.

**** Director & Consultant Diabetologist, Dr Surajeet Patra's Diabetes Clinic, Bhubaneswar, Odisha

***** Chief Clinical Coordinator, Metta Clinic (Metta Care Services) Kolkata.

FIGURE 1

PATHOGENESIS OF SILENT CAD IN DIABETES (1,2,3,4,5,23,43)



CARDIOVASCULAR RISK PREDICTION IN DIABETES

Risk calculators are foundational tools for patient stratification and guiding screening decisions, as demonstrated in Table 1.

TABLE 1

COMMON CARDIOVASCULAR RISK ENGINES USED IN DIABETES (14,15,31,41,46)

Risk Engine	Patient Type	Core Variables (Examples)
UKPDS	T2D	Age, Sex, Ethnicity, HbA1c, BP, Cholesterol/HDL, Smoking, Duration
Swedish Diabetes Register (NDR)	T1D	Age, Smoking, HbA1c, BP, Lipids, Macroalbuminuria, Prior CVD, Duration
Steno Type 1 Risk Engine	T1D	Age, Sex, Smoking, Glycemia, BP, LDL, Albuminuria, eGFR, Activity
QRISK3	T1/2D	Ethnicity (South Asian, Indian), SLE, mental health, chronic disease, CKD, BP, cholesterol, T1/T2D presence
SCORE2/SCORE2-D	T1/2D	Age, Sex, BP, Cholesterol, Region

CVD: cardiovascular disease; HbA1c: hemoglobin A1C; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NDR: National Diabetes Register; UKPDS: United Kingdom Prospective Diabetes Study.

QRISK3 is notable for its inclusivity, having been validated in diverse ethnic groups, including South Asian and Indian populations (10,15,31,47). In contrast, ***SCORE2-D*** is a newer algorithm designed specifically for assessing cardiovascular risk in individuals with diabetes, but it has yet to be validated in Asia-Pacific populations (31). A key limitation of most risk calculators is that they are primarily developed using Western datasets, which raises concerns about their accuracy and applicability in more diverse global populations, underscoring the need for broader validation (14,31,47).

BIOMARKERS AND SEROLOGICAL TESTS

Blood-based markers are increasingly being integrated with clinical predictors to improve the accuracy of cardiovascular risk models. Among these, NT-proBNP has shown strong prognostic value for the development of CAD and heart failure (20,26,47,53). High-sensitivity troponin further enhances risk discrimination, particularly for detecting subclinical CAD and predicting mortality (20,26,47). Genetic markers, including several polygenic risk scores (PRS) targeting genes involved in atherogenesis, have also been developed; these scores have shown particular utility in older populations by improving predictive accuracy beyond traditional cardiovascular risk factors (55). In addition, a range of novel metabolic, inflammatory and lipid markers are currently under investigation for their potential to further refine risk assessment (12,20).

Integration of cardiac biomarkers can fine-tune risk classification, especially in those at borderline/intermediate risk (14,17,20,47).

MODES OF NON-INVASIVE TESTING FOR SILENT CAD

Table 2 presents the diagnostic performance of non-invasive tests for coronary artery disease in individuals with diabetes.

TABLE 2

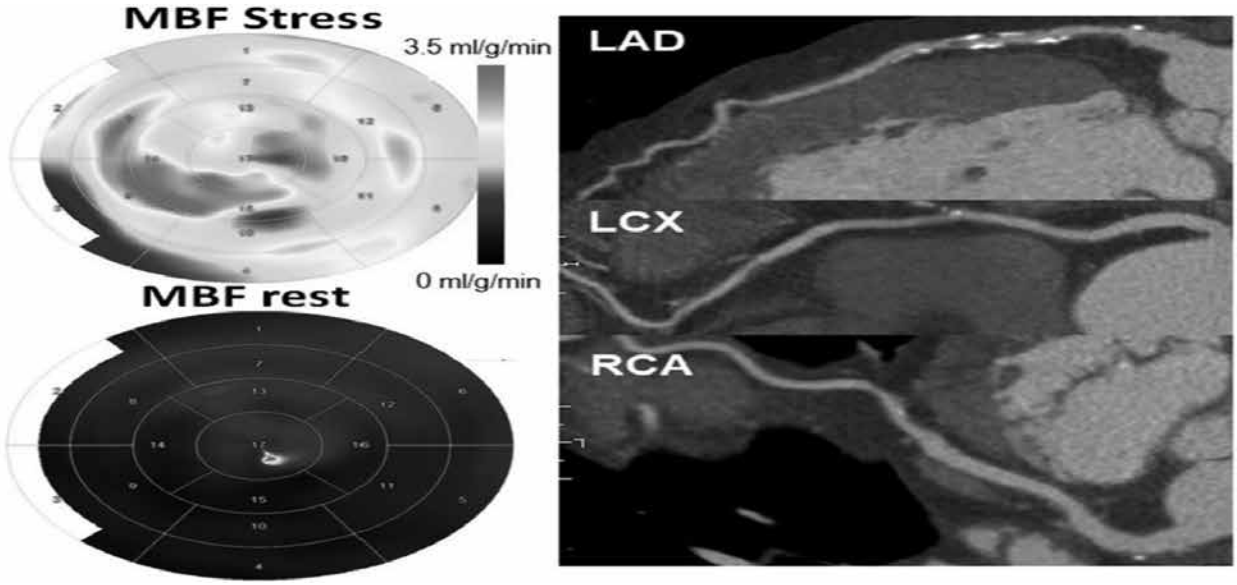
DIAGNOSTIC PERFORMANCE OF NON-INVASIVE CAD TESTS IN DIABETES
(14,16,18,19,22,25,29,30,31,32,33,49,50,53)

Test	Sensitivity (%)	Specificity (%)	Pros	Cons
Exercise ECG	45–61	70–90	Available, low-cost	Low sensitivity, limited in older/comorbid patients
Stress Echocardiography	70–85	77–89	No radiation, higher specificity	Operator-dependent, limited in obese, arrhythmia
SPECT Myocardial Perfusion	73–92	63–88	High sensitivity, detects multi-vessel disease	Radiation, artifact, expense
Pharmacologic Stress SPECT	88–91	75–90	High sensitivity, exercise not required	Radiation, availability
Coronary CT Angiography (CTA)	93–99	64–90	Anatomical detail, very high NPV	Overestimates severity in calcified vessels, contrast/ Rx
Coronary Artery Calcium (CAC) Scoring	N/A	N/A	Risk stratification, noninvasive	Can't distinguish stenosis, no function assessment
MRI Perfusion/Wall Motion	89–92/77–84	76–82/81–89	No radiation, simultaneous anatomy/ function assessment	High cost, limited access

Contemporary meta-analyses continue to verify the value of exercise ECG for its specificity and prognostic value in selected, able-bodied patient populations, confirming its role in guidelines as an initial test for intermediate-risk individuals where functional assessment is desired (79,80, 103).

FIGURE 2

CORONARY CT ANGIOGRAPHY AND POSITRON EMISSION TOMOGRAPHIC (PET) MYOCARDIAL PERFUSION



Coronary CT angiography and positron emission tomographic (PET) myocardial perfusion images in a 62-year-old man with atypical chest pain, diabetes, dyslipidemia and hypertension. Coronary artery calcium (CAC) scan showed moderate CAC score of 210. Coronary CT angiography showed partially calcified atherosclerosis in the left anterior descending, left circumflex and right coronary arteries (LAD, LCX, and RCA, respectively). Maps of myocardial blood flow (MBF) measured by 15 O-water PET showed no significant myocardial ischemia and invasive coronary angiography showed no obstructive CAD. However, based on PET, coronary flow reserve was impaired (1.8), suggesting coronary microvascular dysfunction.

LIMITATIONS

Approximately 50% of individuals with diabetes may be unable to complete exercise-based stress tests due to comorbidities or frailty (24). While advanced imaging modalities such as Coronary CT Angiography (CTA) and Coronary Artery Calcium (CAC) scoring are valuable for detecting anatomical coronary artery disease, they do not always reflect the presence or severity of functional ischemia (32,33,34).

ROLE OF AUTONOMIC NEUROPATHY AND CARDIAC ABNORMALITIES

Cardiac Autonomic Neuropathy (CAN) is a serious complication of diabetes that significantly increases the risk of arrhythmias, sudden cardiac death and silent myocardial ischemia (6,28,46). The diagnosis of CAN typically requires at least two abnormal cardiovascular reflex tests (28). Clinically, the presence of CAN should prompt more aggressive cardiovascular screening and risk assessment, given its strong association with adverse cardiac outcomes (28,46).

CAN is the most studied and clinically important form of diabetic autonomic neuropathy (DAN). It involves damage to the autonomic nerve fibers that control the heart and blood vessels, leading to abnormalities in heart rate control and vascular dynamics. CAN increases myocardial oxygen demand, alters heart rate, reduces myocardial blood flow by increasing coronary vascular tone at stenotic sites, and lowers coronary perfusion pressure during orthostatic hypotension (56,57,58). This results in a higher risk of silent myocardial ischemia (SMI), which is especially prevalent in people with diabetes (PWD). Studies in India show around 40% having SMI and a threefold higher prevalence in those with CAN (59).

The diagnosis of CAN relies on several autonomic function tests rather than a single test. According to a 1992 consensus, three tests - R-R interval variation, Valsalva maneuver and postural blood pressure testing are recommended. Heart rate variability (HRV) is a sensitive and early marker of CAN and can be measured routinely in clinics using standard physiological maneuvers. HRV testing at diabetes diagnosis for T2D or within five years of diagnosis for T1D sets a baseline for annual comparisons, facilitating early detection and intervention. HRV testing may also facilitate differential diagnosis and the attribution of symptoms (eg. erectile dysfunction, dyspepsia, and dizziness) to autonomic dysfunction (Table 3).

TABLE 3

CARDIOVASCULAR AUTONOMIC TESTING (60,61)

Cardiovascular autonomic testing
Tests of predominantly parasympathetic function
• Heart rate variability to deep breathing(ie,supine position with the subject breathing at a fixed rate of six breaths per minute during a six-minute period): Analyzed by the heart rate variability and the expiratory to inspiratory ratio
• Heart rate response to standing(the 30:15 ratio)
• Heart rate response to Valsalva maneuver (the Valsalva ratio)
Tests of predominantly sympathetic adrenergic function
• The beat-to-beat blood pressure response to a Valsalva maneuver (dropin phase 2, the phase 4 overshoot)
• The systolc and diastolic blood pressure change in response to tilt table testing or active standing
Tests of sympathetic cholinergic function
• Quantitative sudomotor axon reflex testing (QSART)
• Thermoregulatory sweat testing (TST)
• Sympathetic skin response (SSR)
Direct assessment of cardiac autonomicintegrity by scintigraphicimaging

A confident diagnosis of CAN usually requires abnormalities in two or more cardiac autonomic function tests (60,61). The diagnostic classification of CAN includes several stages based on the number and severity of abnormal findings (62, 63). Possible or early CAN is defined by the presence of one abnormal cardiovascular reflex test (64). Definite or confirmed CAN is diagnosed when two such tests are abnormal (65). Severe or advanced CAN is characterized by the presence of definite CAN along with orthostatic hypotension-a sudden drop in blood pressure upon standing or being tilted at a 60-degree angle. This is defined as a decrease in systolic blood pressure of at least 20 mmHg or a diastolic decrease of 10 mmHg within three minutes of standing or tilt (66).

CAN is strongly associated with a fivefold increased risk of cardiovascular mortality and its prevalence increases with duration of diabetes and age, rising about 2% per year in T1DM and 6% per year in T2DM (68). Symptoms usually present late; advanced CAN is mostly irreversible with a high 5-year mortality reaching up to 50%, which is worse than many common cancers (67, 69). Early testing is therefore critical to identify reversible stages for timely lifestyle and pharmacologic interventions.

Identification of early CAN using focused diagnostic testing is clearly essential to allow the timely provision of multifaceted lifestyle and pharmacologic interventions at an early stage where CAN is reversible. Early identification of subjects with CAN from routine yearly testing can lead to a strategic reduction in mortality.(70) A recommendation of installation of a CANS 504 Cardiac Autonomic Neuropathy System Analyser (Diabetik Foot Care India Pvt. Ltd.) in every clinic which claims to project as a dedicated clinic treating Diabetes, Obesity, Metabolic Syndrome should be mandatory to routinely conduct this test on every single such case who walks into that clinic assuming that anyone can be potentially an asymptomatic individual with CAD. It is worth noting that usually 20% of them have abnormal CAN and reduced heart rate variation is usually the earliest indicator of CAN

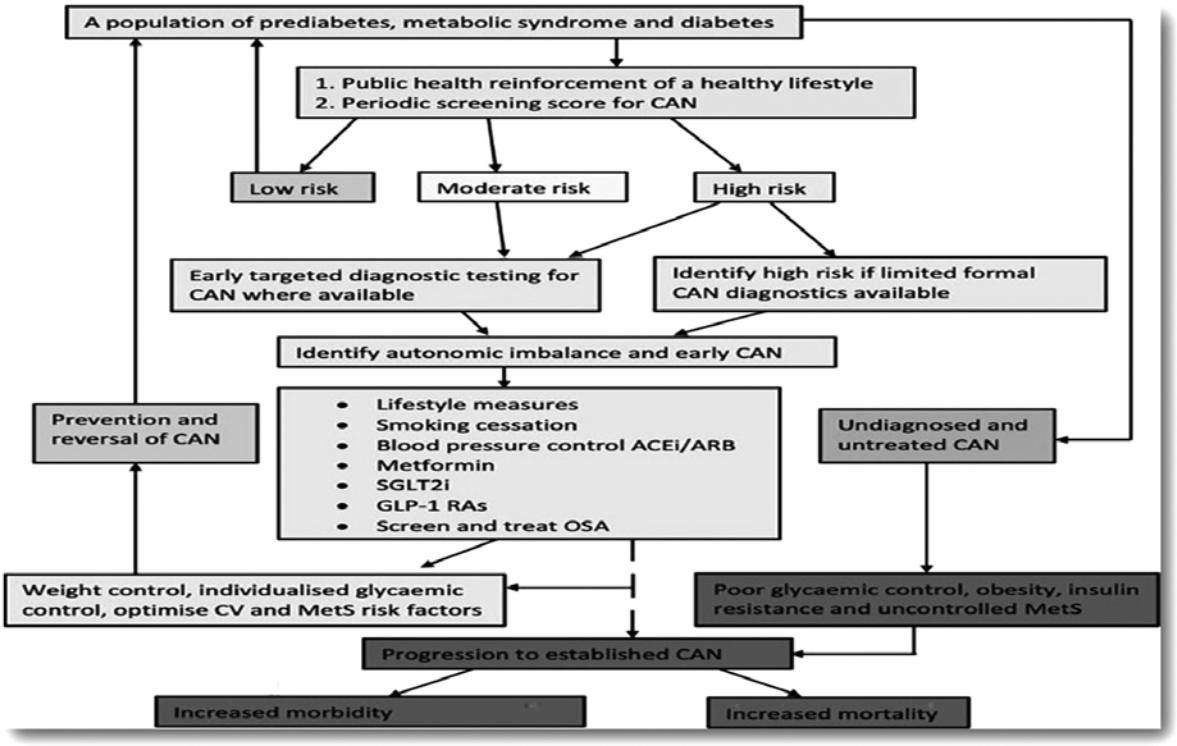
in them. This can predict the HR response while doing the stress exercise ECG to rule out CAD. Individuals with CAN should be screened and receive physician approval for possibly a closely monitored exercise stress test for detection of evidence for CAD or recommendation before exercise initiation as exercise intensity is best prescribed using the HR reserve method with direct measurement of maximal HR.

In summary, CAN is a prevalent, serious and underdiagnosed complication in diabetes that requires routine screening using standardized autonomic tests for early detection, prognosis and management to reduce cardiovascular risk and mortality.

Figure 3 highlights the importance of early recognition of CAN at a reversible stage and a multifaceted approach to its management with both lifestyle and pharmacologic interventions.

FIGURE 3

A PUTATIVE MULTIFACETED TREATMENT STRATEGY REQUIRED FOR THE MANAGEMENT OF CARDIAC AUTONOMIC NEUROPATHY (CAN) IN DIABETES
(59,71,72)



EVIDENCE FROM MAJOR RANDOMIZED TRIALS AND META-ANALYSES

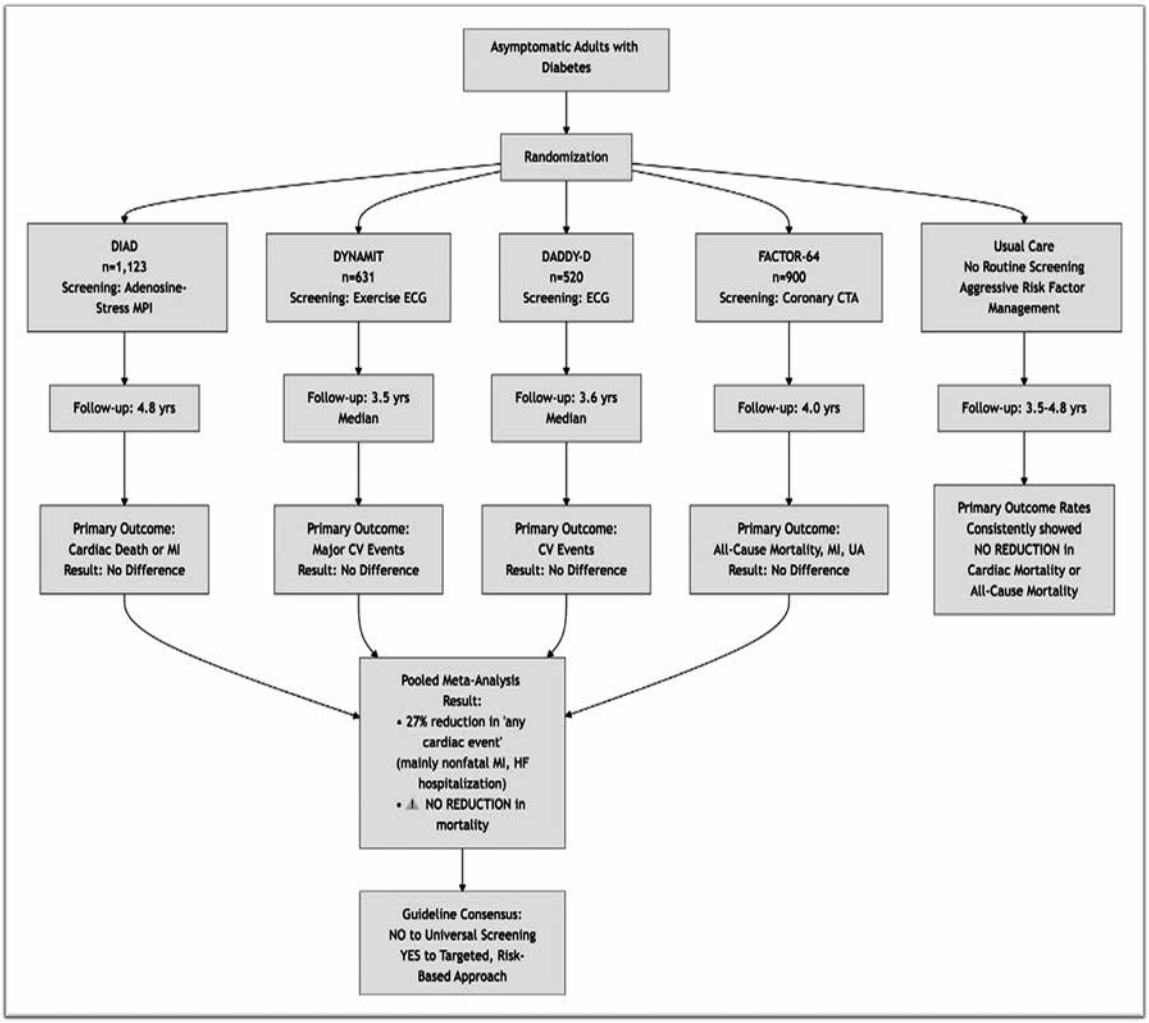
Five major randomized controlled trials (RCTs) systematically evaluated if routine screening improves hard clinical outcomes (9,16,17,29): Figure 4 depicts RCT design and outcomes.

The DIAD study (Young LH, et al.) found no benefit of perfusion imaging-based screening compared to usual care (9,16). Similarly, the DYNAMIT trial showed that exercise ECG-based screening did not reduce major composite cardiovascular events and the DADDY-D trial reported no reduction in cardiovascular events with ECG screening over a median follow-up of 3.6 years (16). The FACTOR-64 study, which used coronary CT angiography for screening, also failed to demonstrate a reduction in all-cause mortality or myocardial infarction (8). While meta-analyses suggest a modest 27% reduction in "any cardiac

event" primarily driven by nonfatal myocardial infarctions and heart failure hospitalizations no significant reductions were observed in cardiac or all-cause mortality (16,17,29,35).

FIGURE 4

SCREENING FOR CAD: RCTS DESIGN AND OUTCOMES (9,16,17,29)



CAD RISK FACTORS: HYPERTENSION, LDL-CHOLESTEROL AND GLYCEMIA

Hypertension, elevated LDL-cholesterol (LDL-C) and dysglycemia remain the primary modifiable risk factors for coronary artery disease (CAD), forming the cornerstone of most risk prediction algorithms like the pooled cohort equations (PCE) and SCORE2 (73,74,75,76,78,83). The pathophysiological link involves endothelial injury, chronic inflammation, and lipid accumulation within the arterial intima, initiating and propagating atherosclerotic plaque. Persistent blood pressure elevation, even within the pre-hypertensive range 120–139/80–89 mmHg, has been confirmed across meta-analyses to accelerate endothelial dysfunction and atherosclerotic plaque formation through increased wall shear stress and potentiation of oxidative stress (74,78,84). Contemporary global datasets from registries like CLARIFY and REACH affirm that approximately one in three CAD patients has hypertension at diagnosis, with poor control (<140/90 mmHg) doubling the risk of subsequent myocardial infarction (78).

The causal, cumulative effect of LDL-C on atherosclerosis is unequivocally supported by randomized trials, Mendelian randomization studies and large-scale meta-prediction frameworks (75,73). The concept of "cumulative LDL-C

exposure" (analogous to "pack-years" in smoking) is critical; long-term even modest elevations significantly increase lifetime risk. Recent integrative models, such as those incorporating polygenic risk scores (PRS) with clinical factors like the UK Biobank risk tool, demonstrate a superior 10-year prediction of incident CAD, identifying individuals with subclinical disease who benefit most from preemptive statin therapy (73, 85). The efficacy of LDL-C reduction is a continuum; for every 1 mmol/L (~39 mg/dL) reduction, major adverse cardiovascular events (MACE) are reduced by approximately 22%, a benefit consistent across drug classes (statins, ezetimibe, PCSK9 inhibitors) and regardless of baseline lipid status (75, 86).

Dysglycemia, from insulin resistance to overt diabetes mellitus, confers a two-to-four-fold increased risk of coronary events. This is mediated not only by hyperglycemia but also by associated dyslipidemia (high triglycerides, low HDL, small dense LDL particles), endothelial dysfunction and a prothrombotic state (76,74,78) (Table 4). The legacy effect of early glycemic control, as demonstrated in long-term follow-ups of trials like UKPDS, underscores the importance of early intervention. Beyond metformin, newer antidiabetic agents with proven cardiovascular benefit, specifically SGLT2 inhibitors (eg. empagliflozin) and GLP–1 receptor agonists (eg. liraglutide, semaglutide), reduce MACE and heart failure hospitalizations through weight loss, blood pressure reduction and likely direct vascular effects, independent of their glucose-lowering efficacy (76, 87).

TABLE 4

MAJOR CORONARY ARTERY DISEASE RISK FACTORS: PREVALENCE AND IMPACT
(76,74,78)

Risk Factor	Prevalence	Odds Ratio	Population Attributable Risk	Notes
Hypertension	33%	2.5	15%	Pre-hypertension accelerates risk
Smoking	39%	3.0	20%	Leading cause of cardiovascular disease
Diabetes Mellitus	41%	2.4	18%	2 to 4 times increased risk, including insulin resistance
Dyslipidemia	37%	2.8	25%	LDL > 100 mg/dL; lipid management decreases major adverse cardiac events
Obesity	18%	1.8	8%	Visceral adiposity is a key mechanism
Family History of CAD	19%	2.2	12%	Risk for premature CAD (men <55 years, women <65 years)
Physical Inactivity	60%	1.6	10%	Less than 150 minutes of moderate activity per week increases risk
Chronic Kidney Disease	8%	3.2	5%	eGFR < 60 mL/min/1.73m² is considered equivalent risk

Additional potent modifiable risk factors; most notably tobacco use (both smoking and vaping), visceral adiposity and physical inactivity remain central across recent meta-analyses (74,78,83). Latest studies also highlight the role of nontraditional risk enhancers. These include chronic inflammatory states (eg. elevated hs-CRP, IL–6), prothrombotic factors (eg. elevated fibrinogen), and psycho-social determinants of health (eg. depression, low socioeconomic status), which are increasingly incorporated into refined risk assessment models (74,76, 88, 89).

SUSCEPTIBLE POPULATIONS REQUIRING

EARLY AND AGGRESSIVE SCREENING

Identifying high-risk cohorts allows for targeted, cost-effective prevention. Younger adults (<45 years), especially those with a family history of premature ASCVD (defined as <55 years in men, <65 years in first-degree relatives), represent a critical group where traditional risk scores often underestimate lifetime risk (73,74,76,80,90). Individuals of South Asian ancestry experience a 3–4 fold higher adjusted risk of CAD and present with disease approximately a decade earlier than other ethnic groups, driven by a higher prevalence of insulin resistance and elevated ApoB-containing lipoproteins (91). Those with genetic dyslipidemias, notably heterozygous familial hypercholesterolemia (HeFH) (prevalence ~1:250) and elevated Lipoprotein(a) [Lp(a)>50 mg/dL (prevalence ~20%)], have a lifelong exposure to high atherogenic particle concentration, justifying screening from childhood or young adulthood (73,76,81,92) (Table 5).

Women-specific risk factors are paramount. Autoimmune inflammatory disorders (eg. Rheumatoid Arthritis, SLE) confer a risk comparable to diabetes, and history of pre-eclampsia, preterm delivery, or gestational diabetes signifies endothelial dysfunction and doubles future CAD risk (75,76,93). Premature surgical menopause without hormone replacement therapy is another significant risk enhancer.

Population-level studies confirm a concerning trend of CAD events in younger populations, with 5–10% of acute MIs occurring before age 45, often associated with polysubstance abuse, high-risk lipid profiles, and genetic predispositions (74,79). Comorbidities like chronic kidney disease (eGFR <60 mL/min/1.73m²) and non-alcoholic fatty liver disease (NAFLD) with significant fibrosis (F2-F4) are now recognized as coronary risk equivalents, with prospective studies linking advanced liver fibrosis to a fourfold increase in cardiovascular mortality (76, 94). The confluence of these factors eg. a young South Asian male with hypertension and a strong family history demands earlier and more aggressive screening, often beginning in the third decade of life (73,76,81, 90).

TABLE 5

HIGH-RISK CAD POPULATIONS (73,76,51,92)

Population	Age at Screening Initiation	Screening Interval	Relative Risk & Notes	Key Risk Factors	Special Considerations
South Asians	Third decade	Annual	3-4 times higher risk	Insulin resistance, Elevated ApoB	High prevalence of metabolic syndrome
Familial Hypercholesterolemia	Childhood / Young adult	Annual	Lifelong exposure to high LDL	LDL >190 mg/dL, Heterozygous FH	Strong emphasis on family screening
Elevated Lp(a)	Young adult	Monitoring (eg. every 5 yrs)	Linear relationship with CAD risk	Lp(a) >50 mg/dL (≈ 20% of population)	Limited treatment options
Pregnancy Complications	Post-pregnancy	Every 2-3 years	~2 times increased CAD risk	Pre-eclampsia, Gestational diabetes	Risk manifests pre-menopause

Population	Age at Screening Initiation	Screening Interval	Relative Risk & Notes	Key Risk Factors	Special Considerations
Autoimmune Conditions	At time of diagnosis	Annual	RA: 1.5-2x risk, SLE even higher	Chronic systemic inflammation	Considered an AHA risk enhancer
Chronic Kidney Disease (CKD)	When eGFR <60	Annual	Coronary artery disease equivalent	eGFR <60 mL/min/1.73m²	Accelerated atherosclerosis
Family History, Premature	Before age 45	Every 2-3 years	Underestimated by traditional scores	Premature ASCVD in 1st-degree relative	5-10% of MIs occur in patients <45

Abbreviations: CAD (Coronary Artery Disease), ApoB (Apolipoprotein B), HeFH (Heterozygous Familial Hypercholesterolemia), Lp(a) (Lipoprotein(a)), P-eclamp (Pre-eclampsia), GD (Gestational Diabetes), RA (Rheumatoid Arthritis), SLE (Systemic Lupus Erythematosus), AHA (American Heart Association), CKD (Chronic Kidney Disease), eGFR (estimated Glomerular Filtration Rate), ASCVD (Atherosclerotic Cardiovascular Disease), MI (Myocardial Infarction)

COMPREHENSIVE ROUTINE CARDIOVASCULAR RISK SCREENING AND RE-ASSESSMENT

Standard practice, as endorsed by ACC/AHA and ESC guidelines, includes an annual review of core clinical parameters: blood pressure, fasting lipid profile (with calculation of non-HDL-C and ApoB), glycemic status (HbA1c or fasting glucose), smoking status, kidney function (eGFR, urine albumin-to-creatinine ratio), BMI, waist circumference and a meticulously updated family history (73,76,78,80,95). Early, systematic screening programs such as those implemented in workplace or community health settings, demonstrably improve the identification and modification of risk factors. This is especially impactful in young adults and high-risk ethnic groups who are less likely to engage with traditional healthcare systems (78).

Beyond quantitative metrics, qualitative visualization techniques have emerged as powerful motivational tools. Showing patients their actual coronary artery calcium (CAC) scan or CCTA images making the subclinical disease "visible" has been shown in randomized trials like but not limited to the one cited to significantly improve medication adherence and lifestyle modification compared to simply discussing numerical risk (77).

Lifestyle factors must be actively queried, not passively recorded. This includes assessing physical inactivity (<150 min/week moderate exercise), poor diet (low in fruits/vegetables, high in processed foods and sugar-sweetened beverages), psychosocial stress (using validated tools like the PHQ–2/9 for depression) and poor sleep quality (eg. sleep apnea symptoms). These are direct targets for behavioral intervention (75,81,96).

While routine resting or exercise ECG is not recommended for asymptomatic low-risk adults due to poor positive predictive value (79), interim risk reclassification is a cornerstone of modern prevention. CAC scoring is a Class IIa recommendation for intermediate-risk or selected borderline-risk patients (Table 6). A CAC score of 0 confers an excellent prognosis and may allow for de-escalation of therapy, while a score >100 (or >75th percentile for age/sex/ethnicity) firmly upgrades risk and justifies more aggressive LDL-C and blood pressure targets (73,80,97).

TABLE 6

CORONARY ARTERY CALCIUM (CAC) SCORING GUIDELINES (ACC/AHA AND ESC)

CAC Score	Risk Category	10-Year Risk	Treatment Recommendation	Follow-Up	Notes
0	Very Low Risk	< 1%	De-escalate statin	Repeat in 5yr if RF	NPV > 99%
1 - 10	Minimal Risk	1 - 3%	Moderate statin	3 - 5 years	Present burden
11 - 100	Mild Risk	3 - 8%	Moderate statin recommended	3 years	Established plaque
101 - 300	Moderate Risk	8 - 15%	High-intensity statin, consider add-on	3 years	Significant plaque
301 - 999	High Risk	15 - 25%	High-intensity statin + add-on therapies	Monitor progression	Extensive plaque
≥ 1000	Very High Risk	> 25%	Max therapy + PCSK9 inhibitor	Annual monitoring	Severe disease burden
> 75th %ile	Adjusted High Risk	Varies	Upgrade risk category	By absolute score	Relative risk important

Abbreviations: RF: Risk Factors, NPV: Negative Predictive Value, PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9 (a class of cholesterol-lowering drugs), %ile: Percentile for age, sex, and ethnicity

STEPWISE CARDIAC DIAGNOSTIC WORK-UP WHEN CAD IS SUSPECTED

Acute Chest Pain (Hours–Days): The Rule-Out Pathway

The initial step remains immediate acquisition of a 12-lead ECG and high-sensitivity cardiac troponin (hs-cTn) testing using validated 0/1-h or 0/3-h algorithms (75,76). The European Society of Cardiology (ESC) 0/1-h algorithm, for example, allows for rapid rule-out (~60% of patients) with a negative predictive value (NPV) >99.5% if hs-cTn is undetectable and the ECG is non-ischemic, enabling safe discharge from the emergency department (98). Patients with elevated troponin levels, dynamic ECG changes, or a high clinical risk score (eg. GRACE score >140) have confirmed acute coronary syndrome (ACS). Those who are hemodynamically unstable require immediate transfer to the catheterization lab for invasive coronary angiography (ICA). Stable patients with non-diagnostic findings but ongoing concern are best triaged with coronary CT angiography (CCTA), which has an exceptional NPV to exclude obstructive CAD (75,76,99).

Stable Symptoms (Weeks–Months), The Ischemia-Guided Pathway

For stable symptomatic patients, the choice of first-line test is guided by the pre-test probability (PTP) of obstructive CAD, now best calculated using updated models that incorporate sex-specific data and avoid overestimation (100).

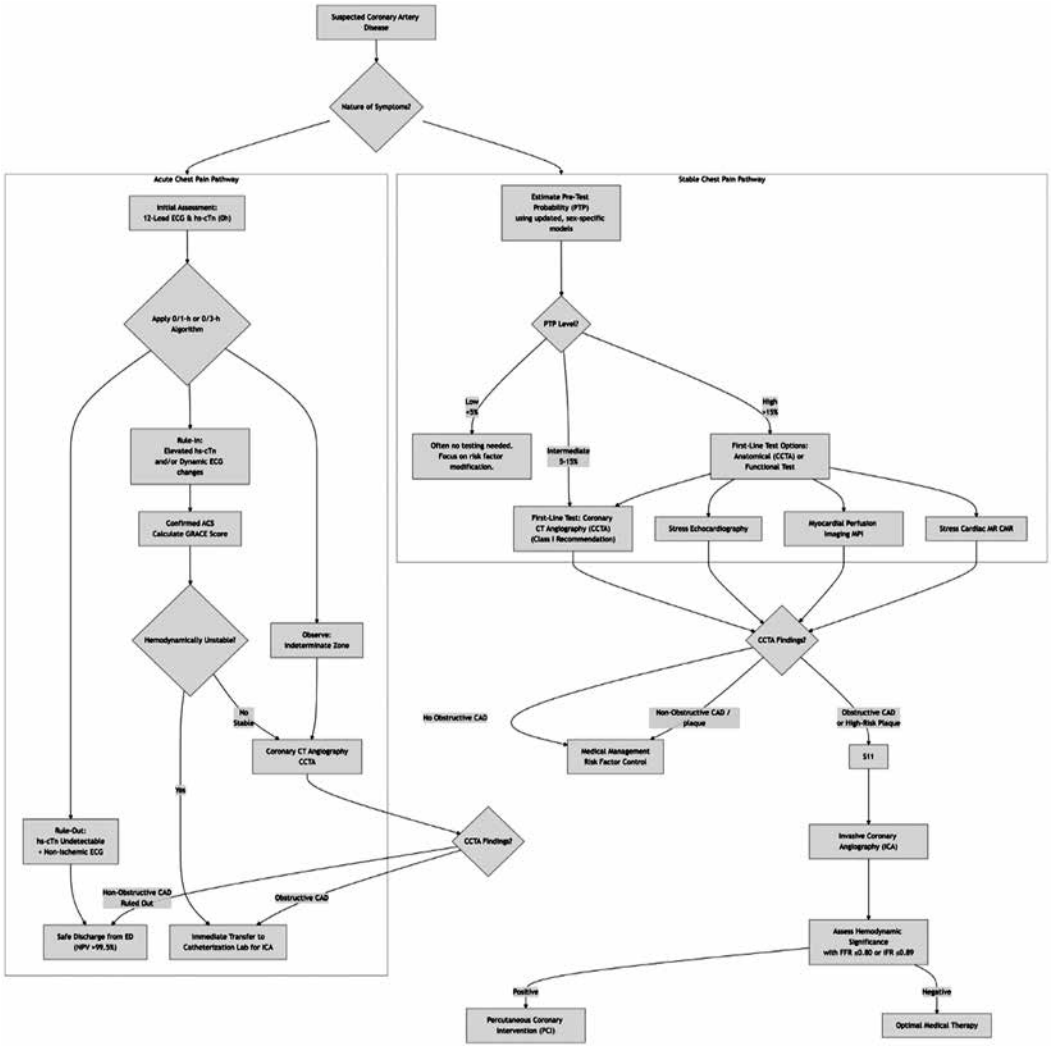
- ***Low PTP (<5%):*** Often no testing is needed; focus on risk factor modification.
- ***Intermediate PTP (5–15%):*** CCTA is the preferred first-line test (Class I recommendation in guidelines) due to its high sensitivity (≥95%) and superior ability to rule-out disease, providing both anatomical and plaque characterization information (non-calcified, calcified, mixed) (76,81, 100).
- ***High PTP (>15%):*** Either anatomical testing with CCTA or functional testing is acceptable. Functional tests include stress echocardiography, myocardial perfusion imaging (MPI with SPECT or PET), or stress cardiac magnetic resonance (CMR). The choice depends on local expertise, availability, patient characteristics (eg. ability

to exercise, body habitus), and the need to avoid radiation (76,82,101).

- Discordant or inconclusive non-invasive results (eg. symptoms with a negative CCTA, or mild ischemia on MPI in a high-risk patient), combined with high clinical suspicion, mandate escalation to the gold standard: invasive coronary angiography (ICA) (Figure 5). Physiology-guided revascularization using fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) is mandatory to assess the hemodynamic significance of lesions of intermediate severity (40–90% stenosis). Revascularization is only beneficial if FFR ≤0.80 or iFR ≤0.89, a strategy proven to improve outcomes and optimize stent placement (76, 102).

FIGURE 5

STEPWISE CARDIAC DIAGNOSTIC WORKUP FOR SUSPECTED CAD
(75,76,98,99,100,102)



Abbreviations: CAD: Coronary Artery Disease, ECG: Electrocardiogram, hs-cTn: High-sensitivity Cardiac Troponin, NPV: Negative Predictive Value, ED: Emergency Department, ACS: Acute Coronary Syndrome, GRACE Score: Global Registry of Acute Coronary Events Score, ICA: Invasive Coronary Angiography, CCTA: Coronary CT Angiography, PTP: Pre-Test Probability, MPI: Myocardial Perfusion Imaging, SPECT/PET: Single-Photon Emission CT / Positron Emission Tomography, CMR: Cardiac Magnetic Resonance, FFR: Fractional Flow Reserve, iFR: Instantaneous Wave-Free Ratio, PCI: Percutaneous Coronary Intervention

PROS AND CONS OF UNIVERSAL SCREENING IN DIABETES

Pros

Identifying occult high-risk coronary artery disease (CAD) enables clinicians to implement targeted risk factor modification and, in select cases, consider revascularization (16,22,27). Additionally, such risk reclassification may inform decisions regarding aspirin therapy, ensuring its use is more appropriately tailored to individual cardiovascular risk profiles (49).

Cons

Despite its potential benefits, screening for coronary artery disease in asymptomatic patients with diabetes has not shown a significant impact on mortality or major cardiovascular events in randomized controlled trials (16,17,27,42). Additionally, it increases healthcare costs and radiation exposure, and may lead to unnecessary testing or interventions (8,27,30). Most individuals with diabetes are already eligible for intensive multifactorial risk-reduction strategies, limiting the added value of routine screening (14,41,46). Moreover, such screening often results in only minor adjustments to medication regimens or vessel-level interventions (32,41).

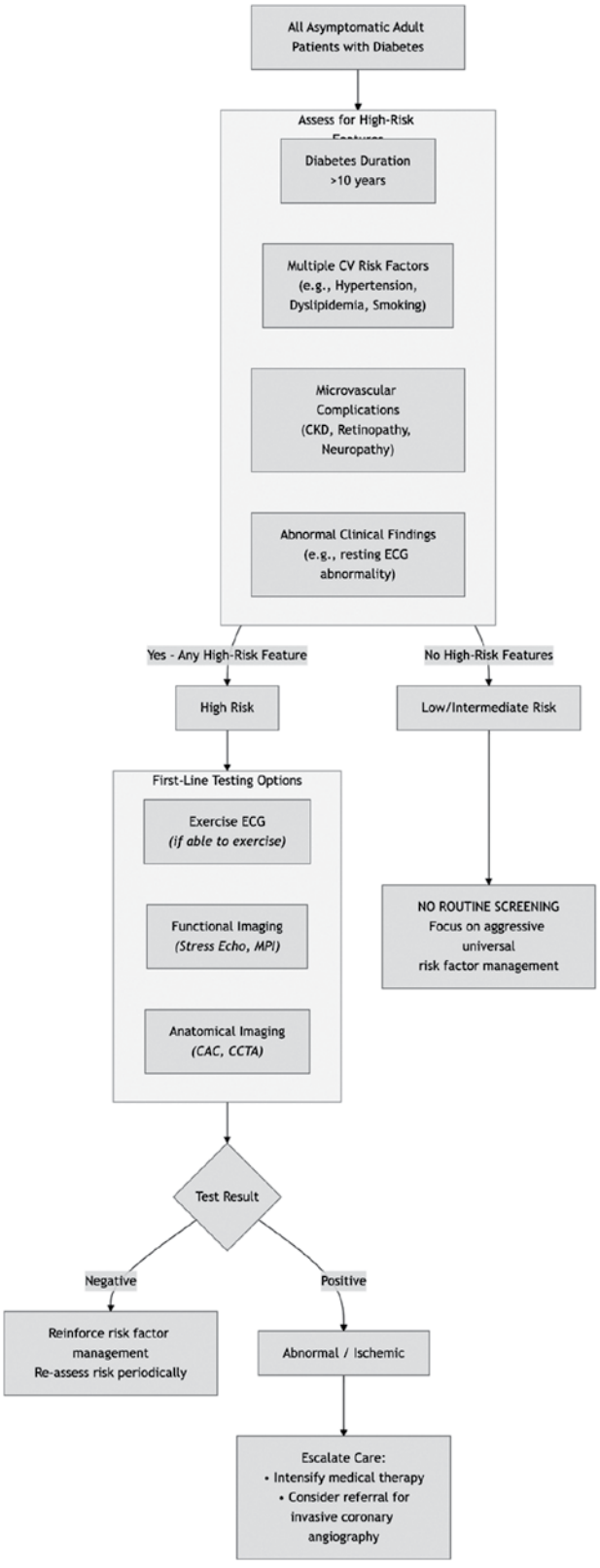
GUIDELINE AND POSITION STATEMENT CONSENSUS

Universal cardiovascular screening in asymptomatic individuals with diabetes is not recommended by major guidelines, including those from the American Heart Association (AHA) (15,22,35), the American Diabetes Association (ADA) (41) and the European Society of Cardiology (ESC) (7,22,28,34).

However, targeted screening may be considered in patients with a diabetes duration of 10 years or more, those with multiple cardiovascular risk factors such as hypertension, dyslipidemia, or a family history of heart disease, as well as individuals with chronic kidney disease, abnormal ECG or physical exam findings. Screening may also be appropriate for patients with known autonomic neuropathy or existing microvascular complications (15,22,28,46). (Figure 6)

FIGURE 6

PRACTICE GUIDELINE FLOW DIAGRAM: RISK-STRATIFIED SCREENING IN DIABETES (15,22,28,46)



DIAGNOSTIC YIELD: WHO SHOULD BE SCREENED?

Table 7 shows Guideline-based, risk-stratified testing which offers maximal diagnostic yield.

Low/intermediate risk: No screening; focus on universal risk factor management.

High-risk asymptomatic: Consider initial exercise ECG (resource constraints) or functional imaging.

Positive/abnormal results: Escalate to CTA/ CAC or invasive angiography as indicated.

TABLE 7

PRACTICAL DIAGNOSTIC ALGORITHM FOR SILENT CAD IN DIABETES

(15,22,32,46)

Step	Action	When to Apply
1	Routine cardiovascular risk assessment (eg. QRISK3)	Initial evaluation of all patients with diabetes
2	Add biomarkers and resting ECG	If patient is at intermediate or high cardiovascular risk
3	Functional imaging (eg. stress ECG, stress echo, MPI)	If patient develops symptoms or risk profile escalates
4	Anatomical imaging (eg. CTA or CAC scoring)	If cardiovascular risk remains uncertain after previous steps
5	Invasive coronary angiography	If noninvasive tests are positive or inconclusive

LIMITATIONS AND FUTURE DIRECTIONS

Key Barriers

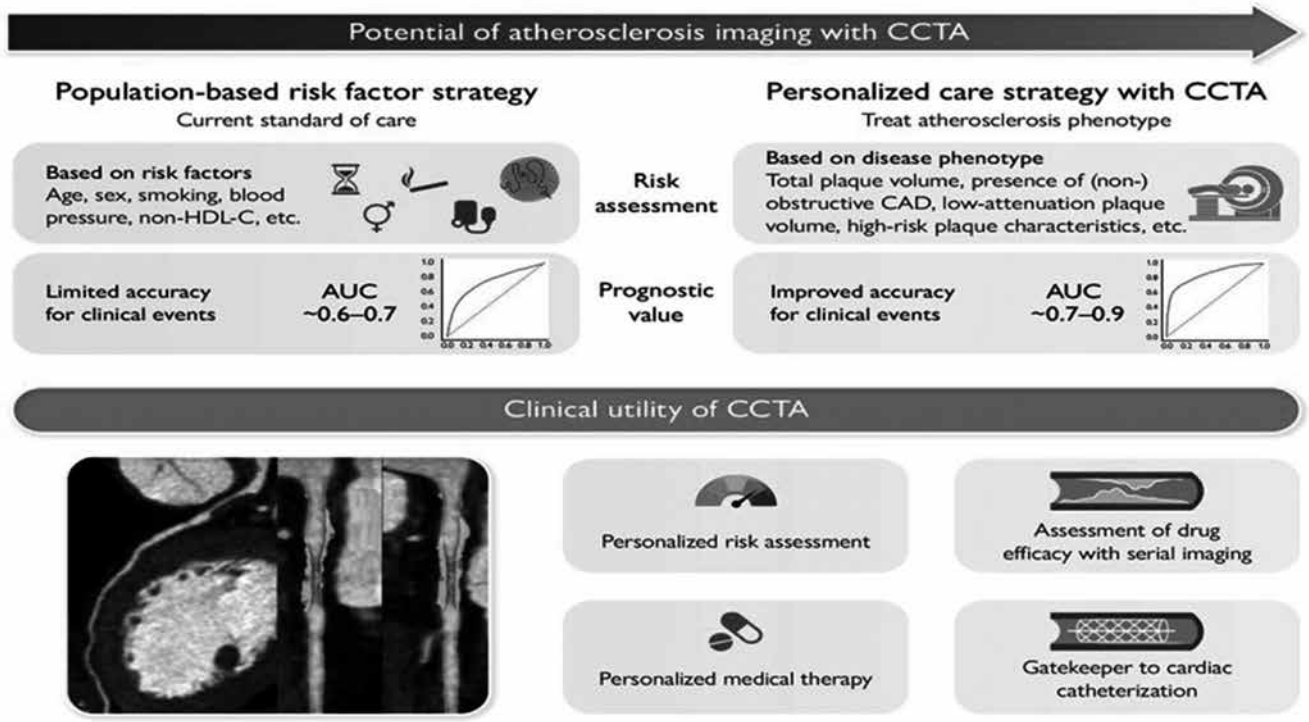
Barriers to effective cardiovascular screening in individuals with diabetes include limited feasibility of certain tests, particularly in older, frail, or comorbid patients who may not tolerate exercise-based assessments. Anatomic imaging can also lead to overdiagnosis and overtreatment, identifying lesions that may not be clinically significant. Additionally, the high cost and limited availability of advanced diagnostic resources pose significant challenges, especially in low-income and resource-limited settings. Furthermore, many widely used risk prediction tools developed in European and North American populations may not accurately reflect cardiovascular risk in South Asian, African or Indigenous populations, limiting their generalizability and effectiveness in diverse global contexts (10,14,15,31,47).

Innovation Frontiers

Advancements in personalized medicine are paving the way for more precise cardiovascular risk assessment in individuals with diabetes. Innovations such as cardiac genetics, metabolomics, and machine learning (ML)-driven algorithms applied to electronic health records are being explored to enhance prediction and prevention strategies (14,15,20,26). Ongoing studies like DANE-HEART and SCOT-HEART 2 aim to further clarify the role of advanced screening and individualized interventions (45). Additionally, biomarker panels that integrate proteomics and lipidomics hold promise for improving noninvasive detection of subclinical cardiovascular disease, potentially transforming future risk stratification and management approaches (12,20) (Figure 7).

FIGURE 7

POTENTIAL OF ATHEROSCLEROSIS IMAGING WITH CCTA (54)



CONCLUSION

CAD in diabetes poses persistent public health and clinical challenges, with up to 60% of disease silent and discovered only on active screening/investigation (6,9,12,32). Universal screening for coronary artery disease in individuals with diabetes has not been shown to improve all-cause or cardiovascular mortality in most randomized studies. As a result, a targeted, risk-based screening approach is considered more pragmatic, focusing on those with a longer duration of diabetes, multiple cardiovascular risk factors, or evidence of involvement of other organs. Regardless of screening outcomes, routine and aggressive management of cardiovascular risk factors such as blood pressure, cholesterol and glycemic control remains the cornerstone of prevention. Emerging innovations in imaging techniques, biomarkers and risk prediction models may soon enable more personalized approaches to the detection and prevention of cardiovascular disease in this high-risk population.

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QUESTIONS AND ANSWERS

Q. What are the frequently used medications which need to be used cautiously in borderline kidney failure (eGFR ml/min/1.72 m²)

A. Once the glomerular filtration rate (GFR) is less than 60 ml/min, the pharmacokinetics of antidiabetic drugs may be altered. Sulfonylurea and glinide therapies are associated with a risk of hypoglycaemia which is increased in the presence of renal impairment. Most sulfonylureas must be discontinued once GFR is <60 ml/min. Some glinides may be continued beyond this threshold, in particular repaglinide and glipizide which may be used in on dialysis. In the absence of comorbidities, metformin can be continued at a lower dose until a GFR of 45 ml/min, but must be withdrawn in case of dehydration or during administration of a nephrotoxic drug, including dyes for radiological investigations. Glitazones may worsen water and sodium retention in patients with renal impairment. The pharmacokinetics of all DPP-IV inhibitors except linagliptin are altered with impaired renal function. GLP-1 agonists are contraindicated in moderate to advanced kidney disease.

For individuals with an eGFR between 30–45 mL/min/1.73 m², the following medication adjustments and precautions should be considered to ensure safe and effective glycemic and comorbidity management:

- Continue or commence nateglinide or repaglinide. Advise people to monitor their post-prandial glucose, 2 hours after taking the medication and to take precautions when driving.
- Continue or commence metformin with caution and explain the risks and benefits to the person. Use lowest dose that achieves glycemic control (suggest a 50% dose up to 1,000 mg/day). Additionally, closely monitor renal function (every 3 months).
- Lixisenatide is to be used 'with caution' in people with a creatinine clearance of 30-50 mL/min and Bydureon TM should be discontinued.
- Reduce dose of sitagliptin to 50 mg daily, vildagliptin to 50 mg once daily, alogliptin to 12.5 mg daily and saxagliptin to 2.5 mg daily. There is no dose reduction needed for linagliptin. Vildagliptin has limited data and it should be used with caution.
- Canagliflozin 100 mg daily may be commenced for reno-protection. Dapaglifozin 10 mg daily may be initiated and/or continued for heart failure.

Q. Are new anti-obesity medications effective in reducing the incidence of diabetes?

A. Diabetes is common among individuals with obesity and managing obesity is a key step in preventing the development of diabetes. Traditionally, the foundation of obesity treatment has been lifestyle modification, which includes a reduced-calorie diet, increased physical activity, and behavioral interventions. However, to achieve meaningful weight loss, pharmacotherapy is often necessary along with lifestyle changes.

Some drugs bring about reduction in use of diabetes medications leading to weight loss such as orlistat and phenteramine/topiramate. Semaglutide, a glucagon-like peptide-1 (GLP-1) analogue, is effective in promoting weight loss and diabetes management. Similarly, liraglutide is another GLP-1 analogue that works by activating the GLP-1 receptor.

Tirzepatide, a dual GLP-1 and GIP receptor agonist, is approved for treating obesity (BMI $\geq$ 30) or overweight (BMI $\geq$ 27) in individuals with at least one weight-related comorbidity. It is the first medication of its kind that acts as a dual agonist at both the GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptors. Tirzepatide is administered once weekly via subcutaneous injection, with available doses of 2.5, 5, 7.5, 10, 12.5 and 15 mg.

Semaglutide and tirzepatide has a central effect on the brain and minimizes the appetite. In the SURMOUNT 1 trial, adults with prediabetes and obesity who took tirzepatide experienced a 94% reduction in progression to Type 2 diabetes compared to a placebo over 176 weeks (3 years). Hence, newer anti-obesity medications like tirzepatide have been shown to dramatically reduce the risk of developing Type 2 diabetes. Other GLP 1 therapies (like semaglutide and liraglutide) also improves metabolic health and likely lowers the risk of diabetes over time.

Dr. Dina Mithani

RECIPES

QUINOA CHIA PUDDING

INGREDIENTS

60 gm Quinoa
5 gm Chia seeds
125 ml unsweetened almond milk
30 gm grated Carrot
10 gm Nuts (walnuts & almonds)
¼ tsp Cinnamon powder
A few drops of Stevia (optional)

METHOD

- Start by cooking the quinoa. Place it in a sieve and rinse thoroughly under cold running water. Transfer the rinsed quinoa to a saucepan, add 400ml of cold water and a pinch of salt. Bring to a boil over medium heat, then lower the heat and let it simmer gently for 10–15 minutes, until the quinoa is tender and all the water has been absorbed.
- In a jar or bowl, mix cooked quinoa, chia seeds, almond milk, cinnamon, grated carrot and sweetener if required.
- Stir well to combine.
- Cover and refrigerate overnight (6–8 hours).
- In the morning, top with nuts before serving.

PROVIDES 2 SERVING

Nutritional Information Per Serving

Energy (kcals)	Protein (grams)	Carbohydrate (grams)	Fat (grams)	GI
120	10	12	5	Low

SPECIAL FEATURE

- Fibre-rich
- Low Glycemic Index

Jincy Sajan

SOYA KEBAB SALAD

INGREDIENTS

50 gm Soya chunks
30 gm Sattu (roasted Bengal gram flour)
10 gm Oats powder
30 gm Carrot (grated)
30 gm Onion (chopped)
50 gm skim Curd
1 tsp Coriander powder
1 tsp Cumin powder
1 tsp Flax seed
1 tsp Lemon juice
2 no. Green chilli (finely chopped)
2 cloves Garlic (chopped/minced)
1 tsp Ginger (grated)
A few Coriander leaves
Garam masala to taste
Red Chilli powder to taste
Black pepper powder to taste
Salt to taste

FOR THE SAUCE:

50 gm skim Curd/Yogurt
50 gm Carrot (grated)
50 gm Onion (chopped)
1 tsp Jeera powder
1 tsp Groundnut oil
1 tsp Lemon juice (optional)
Salt to taste

METHOD

Pre-preparation:

- Add the soya in boiling water and let it cook for 10 minutes. Strain the soya and squeeze out the excess water.
- Grind the soya.
- Preheat the air fryer at 180°C for 10 to 15 minutes

Preparation:

- In a large bowl, add the ground soya, all the vegetables, curd, sattu, oats and spices.
- Taste and adjust the seasonings.
- Form small kebabs from the mixture. Brush lightly with oil.
- In an air fryer, add the kebabs, let them cook for 30 minutes at 180°C until golden brown (flip halfway).
- Alternatively, can pan-fry using a non-stick pan with minimal oil. Cook until crisp on both sides.
- For the sauce, Add all the ingredients to a bowl.
- Add the kebabs and serve them.

PROVIDES 2 SERVING

Energy (kcals)	Protein (grams)	Carbohydrate (grams)	Fat (grams)	GI
120	10	12	5	Low

SPECIAL FEATURE

- Protein-rich
- Low Glycemic Index

Harshini Thakur

HOW KNOWLEDGEABLE ARE YOU?

1. **Which of the following measures does not help to prevent diabetes complications?**
   A. Controlling blood glucose
   B. Controlling blood pressure and blood lipids
   C. Eliminating all carbohydrates from the diet
   D. Prompt detection of diabetic eye and kidney disease
2. **Proliferative retinopathy is often treated using:**
   A. Tonometry
   B. Fluorescein angiogram
   C. Antibiotic
   D. Laser surgery
3. **Which of the following diabetes drugs acts by decreasing the amount of glucose produced by the liver?**
   A. Sulfonylurea
   B. Meglitinide
   C. Biguanide
   D. Alpha-glucosidase inhibitor
4. **The benefits of using an insulin pump include all of the following except:**
   A. By continuously providing insulin they eliminate the need for injections of insulin
   B. They simplify management of blood sugar and often improve HbA1C
   C. They enable exercise without compensatory carbohydrate consumption
   D. They help with weight loss
5. **Diabetic neuropathies are diagnosed using all of the following except:**
   A. Nerve conduction studies or electromyography
   B. Ultrasound
   C. Foot examination
   D. Minnesota Mutiphasic Personality inventory (MMPI)
6. **What is the best strategy to minimise incidence of hypoglycemia in Type 2 diabetes mellitus and achieve optimal glycemic control?**
   A. Use Premix insulin twice a day
   B. Use Prandial insulin 3 times a day
   C. Use basal plus bolus therapy with insulin as sensitizer
   D. Use basal plus bolus therapy
7. **Which oral drug is safe to use in pregnancy with diabetes?**
   A. Pioglitazone
   B. Glibenclamide
   C. Gliclazide
   D. Repaglinide
8. **What are the Frequent side effects of SGLT2 inhibitors?**
   A. Reduced e-GFR
   B. Genital Mycotic infection
   C. Urinary tract infection
   D. Euglycemic ketoacidosis
9. **Which of the following is the major biochemical abnormality found in HONKS?**
   A. Water deficit
   B. Acidosis
   C. Insulin Insufficiency
   D. Sodium deficiency
10. **Long term amelioration of pain of sensory diabetic neuropathy is best achieved by?**
    A. Parenteral Vitamin B12
    B. Optimal Glycemic control
    C. Gabapentin with B12
    D. Aldose reductase inhibitor

ANSWERS:

1.	C	2.	D	3.	C
4.	D	5.	B	6.	D
7.	B	8.	B	9.	B
10.	B				

MYTHS AND FACTS

Myth 1: Taking insulin leads to weight gain and worsens diabetes.

Fact: Insulin therapy often leads to weight gain in people with both Type 1 and Type 2 diabetes. This weight gain can be significant and may increase the risk of cardiovascular problems. Concerns about gaining weight can make it more difficult for individuals to begin or maintain insulin treatment. Weight gain associated with insulin use can occur for several reasons: when blood sugar levels drop too low without a corresponding reduction in food intake, when individuals eat more to prevent or treat low blood sugar, or due to the way insulin functions when administered as an injection.

Body weight gain

Patients with Type 2 diabetes, insulin resistance and obesity are particularly susceptible to insulin-associated weight gain, particularly if a high-dose insulin is required. Patients should be aware of this risk and counseled on diet and lifestyle modifications to achieve body weight maintenance or initiate weight loss.

Multiple factors may contribute to weight gain, such as dietary indiscretion, reduced glycosuria following improved glycemic control after insulin initiation, excessive snacking to prevent hypoglycemia, overtreatment of hypoglycemic events and the adoption of overly tight glycemic targets.

Magnitude of weight gain

The magnitude of weight gain depends on both the intensity of the insulin regimen and diet. In the United Kingdom Prospective Diabetes Study (UKPDS), the average weight gain after 10 years of insulin therapy was approximately 7 kg for patients with Type 2 diabetes, with the most rapid weight gain occurring early after insulin initiation. Less intensive therapy with either insulin or a sulfonylurea was associated with a 3.5 to 4.8 kg weight gain at three years versus no change with metformin monotherapy. Weight gain with basal insulin alone generally appears modest.

However, there are ways to reduce weight gain from insulin. These include taking less insulin by eating healthy and exercising or using other medicines that help with weight, like metformin. Insulin plans that try to act like the body's normal insulin can also help use insulin more effectively. A new type of insulin called insulin detemir seems to not cause as much weight gain. Understanding how this works could help explain the link between insulin and weight.

Myth 2: Certain antidiabetic agents have been associated with renal impairment.

Fact: Diabetes increases the risk of developing chronic kidney disease (CKD) by approximately 2.6 times and triples the risk of death due to renal causes. A significant proportion of individuals with diabetes mellitus will eventually experience impaired kidney function. When the estimated glomerular filtration rate (eGFR) drops below 60 ml/min, a reassessment of antidiabetic therapy becomes essential. At this stage, some oral antidiabetic medications are contraindicated, while others require dose adjustments. However, despite clinical recommendations, these dose modifications are often not implemented.

As kidney function declines, the risk of hypoglycemia increases, especially due to the altered clearance of antidiabetic drugs. In fact, hypoglycemia from diabetes medications is among the top four causes of hospital admissions for adverse drug reactions in the elderly. For this reason, regular monitoring of kidney function at least once a year is critical.

When eGFR falls below 60 ml/min, the pharmacokinetics of many antidiabetic drugs change. Sulfonylureas and glinides carry a heightened risk of hypoglycemia in the setting of renal impairment. Most sulfonylureas should be discontinued when GFR is below 60 ml/min. Some glinides, such as repaglinide, may still be used, even in patients undergoing dialysis.

Metformin may be continued cautiously at reduced doses until GFR falls below 45 ml/min, provided no other comorbidities are present. It must be discontinued in cases of dehydration or during the

administration of nephrotoxic agents, including contrast dyes used in imaging procedures.

Glitazones can exacerbate fluid retention and are thus risky for patients with renal impairment. Additionally, all DPP-4 inhibitors except linagliptin require dose adjustments due to altered drug metabolism in CKD. Among these, only sitagliptin, saxagliptin, and linagliptin are considered suitable for use in advanced kidney disease, although clinical experience remains limited. GLP-1 receptor agonists are contraindicated in moderate to advanced stages of renal impairment.

Myth 3: Exercise can completely cure diabetes.
Fact: Exercise plays a vital role in the management of both Type 1 and Type 2 diabetes, though it should not be considered a standalone cure for either condition. Its benefits are extensive, influencing blood glucose regulation, cardiovascular health, and overall well-being. However, the underlying causes of Type 1 and Type 2 diabetes differ, which affects how exercise contributes to their management.

In Type 1 diabetes, the immune system destroys the insulin-producing beta cells in the pancreas, resulting in a lifelong dependence on insulin therapy. While exercise cannot replace the need for insulin, it provides important complementary benefits. Regular physical activity enhances insulin sensitivity, allowing the body's cells to utilize glucose more effectively, which can lead to improved blood sugar control and reduced insulin requirements. Exercise also supports cardiovascular fitness, helps maintain a healthy body weight, and reduces the risk of diabetes-related complications.

In Type 2 diabetes, the primary issue is insulin resistance, often associated with factors such as obesity, poor diet, and sedentary lifestyle. Exercise is a cornerstone of Type 2 diabetes management because it helps combat insulin resistance directly. During and after physical activity, muscle contractions stimulate glucose uptake from the bloodstream independent of insulin action. Over time, consistent exercise enhances the body's ability to use insulin more efficiently, thereby lowering blood glucose levels. Combined with a balanced diet and weight management, regular exercise can even lead to remission in some individuals, particularly in the early stages of the disease.

Furthermore, exercise contributes to overall metabolic health by improving lipid profiles, lowering blood pressure, and reducing systemic inflammation all of which are important for preventing cardiovascular complications commonly associated with diabetes. Both aerobic exercises (such as walking, cycling, and swimming) and resistance training (like weightlifting or bodyweight exercises) are effective in improving glucose regulation and insulin action.

In summary, while exercise cannot cure diabetes, it is an essential and powerful tool in managing the condition. When combined with appropriate medical treatment, healthy eating and lifestyle modifications, regular physical activity can greatly enhance quality of life and long-term outcomes for people living with both Type 1 and Type 2 diabetes.

Jayshri Jain

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- o Organizational Activities as Office Bearer

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