Redefining the strategies to prevent Cardiorenal Complications of Diabetes.

Abstract: Diabetes is a significant health concern in our country India. The country has a high prevalence of both type 1 and type 2 diabetes. Factors contributing to this include a growing population, genetic predisposition, unhealthy lifestyle choices, and poor access to healthcare in some areas. Diabetes is expected to continue to grow exponentially. Milder forms of Type 1 Diabetes Mellitus like LADA- latent autoimmune diabetes of adulthood, and various other specific forms of Diabetes like MODY - Maturity Onset of Diabetes of Young, are on the rise. It's an upward trajectory in India due to factors like urbanization, sedentary lifestyle, and dietary changes. While diabetes present significant challenges in India's future, proactive measures, technological, advancements and focus on prevention and patient centered care can help mitigate its impact and improve the quality of life for individuals living with diabetes.

Diabetes can lead to various devastating complications, including:

1. Coronary Artery Disease (CAD): Diabetes increases the risk of atherosclerosis in the coronary arteries, leading to CAD. This can result in angina or even silent heart attacks.
2. Diabetic Kidney Disease (Diabetic Nephropathy): This is one of the most common and serious renal complications of diabetes. Over time, high blood sugar levels can damage the small blood vessels and glomeruli in the kidneys, impairing their ability to filter waste and excess fluids from the blood. This condition can progress to chronic kidney disease (CKD) and ultimately lead to kidney failure.
3. Heart Failure and Arrhythmias: Uncontrolled sugars can damage the heart muscle, leading to heart failure and cardiomyopathy where the heart cannot pump blood effectively.
4. Stroke: Diabetes is a significant risk factor for stroke due to its impact on blood vessels and increased risk of blood clots.
5. Hypertension (High Blood Pressure): Diabetes often coexists with high blood pressure,which further stresses the heart and blood vessels and a combination of both Diabetes and Hypertension accelerates kidney damage.
6. Peripheral Artery Disease (PAD), Peripheral Neuropathy: Diabetes can lead to the narrowing of blood vessels in the legs and feet, causing poor circulation, pain, and sometimes gangrene.
7. End-Stage Renal Disease (ESRD): Uncontrolled sugars also commonly leak protein in the urine causing proteinuria.If diabetic nephropathy progresses without proper management, it can lead to ESRD. This stage may require dialysis or a kidney transplant.
8. Ocular complications include premature cataracts, non proliferative and proliferative retinopathy and Glaucoma.
9. Diabetes also commonly cause peripheral neuropathy and autonomic dysfunction.

For Type 1 Diabetes Mellitus, The Diabetes Control and Complications Trial (DCCT), long-term therapeutic study involving patients with Type 1 diabetes Mellitus showed that near normalization of blood glucose resulted in slowing of progression of micro vascular and

neuropathic complications. Preventative Clinical trials of humanized monoclonal antibodies against CD3, hOKT- 3gamma (teplizuman) and ChAglyCD3 (otelixizumab) delayed the decline of insulin production in patients with newly detected type 1 diabetes.

For Type 2 Diabetes Mellitus, The United Kingdom Prospective Diabetes Study (UKPDS), a multi centre study reported intensive treatment with Metformin, sulfonylureas, combination of both or insulin achieved an HbA1c of 7% reduced risk of retinopathy and nephropathy. Tight control of BP greatly reduced the risk of micro vascular disease and stroke. Every 10mmhg decrease in mean systolic Blood pressure was associated with 11% reduction in risk for MI.

The Diabetes Prevention Program reported intervention with a low fat diet and 150minutes of moderate exercise per week reduced the risk of progression to Type 2 Diabetes by 71% Preventing cardiorenal complications in diabetes involves a comprehensive approach that addresses both cardiovascular (heart) and renal (kidney) health. Early detection and timely intervention are key to preventing or slowing the progression of complications in diabetes.

Certainly, redefining strategies to prevent complications of diabetes involves a fresh and proactive approach to improve outcomes. Here are some innovative strategies and concepts in diabetes management:

1. *Dietary changes* – The fundamental element is a well balanced nutritious diet. The macro and micro nutrient proportions should be individualized based on the metabolic goals of the patient. Limiting the carbohydrate intake and replacing with monounsaturated fats such as nuts and avocados can help lower Triglycerides and increase HDL. In Obese patients, caloric restriction is the mainstay. Saturated fats should be limited to less than 10% of daily calories. Meal planning and correct order of eating a meal (fiber first – protein next – fat next – carbohydrates last) must be emphasized.

   The glycemic index of food items must also be explained to the patients. Eating low glycemic – less than 50, foods (legumes, fruits, vegetables) results in lower glucose levels after meals. It is further lowered in the presence of fats and proteins. High glycemic (more than 70) index foods include white rice, white bread must be avoided.

   Artificial sweeteners like sucralose, aspartame, rebiana, sachharin may be used, as none increase the plasma glucose levels. Sugar alcohols like xylitol, sorbitol, mannitol, maltitol commonly labeled as ‘sugar free’ are used as sweeteners and bulking agents.

2. *Weight reduction* – A combination of caloric restriction, increased exercise and behavior modification is preferred. For selected patients, medical and surgical options are considered. The GLP -1 receptor agonists are prescribed for weight loss (Liraglutide, semaglutide). Patients with type 2 diabetes without obesity frequently have increased visceral adiposity – metabolically obese with normal body weight. Resistance training helps in such patients.

3. *Individualized glycemic goal and therapeutic plan* – Maintaining blood sugars within target limits is of utmost importance in preventing complications. The American Diabetes

Association prefers a patient centered approach and suggests that the goal is to achieve an HbA1c as close to normal as possible without significant hypoglycemia. In most individuals, the target HbA1c should be <7%. A higher HbA 1c goal may also be appropriate for the very young or old or in individuals with limited life span or comorbid conditions.

To tailor diabetes treatments and prevention strategies to an individual's unique genetic makeup, lifestyle, and metabolic profile, we use methods such as

- *Self monitoring of blood glucose* - Individuals with type 1 DM or individuals with type 2 DM taking multiple insulin injections each day should measure their blood glucose >3 times/day, although the optimal frequency of SMBG has not been clearly defined.
- *Continuous Glucose monitoring* - Glucose sensors which detect interstitial glucose are placed subcutaneously and are replaced every 3–14 days. These help in detecting time in a glycemic range (TIR), the ambulatory glucose profile, the amount of time in the hypoglycemic range, and the glucose management indicator (GMI). For individuals using CGM, maximizing time-in-range 70–180 mg/dL, representing normoglycemia, while minimizing time-below-range <70 mg/dL, representing hypoglycemia, are shorter-term targets of therapy.

4. *Pharmacotherapy* for treatment of hyperglycemia - Most physicians and patients prefer oral glucose-lowering agents as the initial choice. Any therapy that improves glycemic control reduces “glucose toxicity” to beta cells and may improve endogenous insulin secretion is preferred. Medications that primarily increase insulin secretion include Sulfonylureas (Glimepride, Glyclazide), Meglinitides analogues (Repaglinide, Nateglinide), Medications that lower glucose by their actions on liver/ muscle and adipose tissue include Metformin, Thiazolidinediones (Pioglitazone, Rosiglitazone), medications that affect glucose absorptioninclude Acarbose, Miglitol, Incretins like Liraglutide, Semaglutide, DPP4 Inhibitors (Vildagliptins, Sitagliptins), SGlT2 Inhibitors (Empaglifloxin,Dapagliflozin) .

   Insulin therapy is the mainstay for Type 1 Diabetes Mellitus and in some case of Type 2 in combination with oral medications. The goal is to design and implement insulin regimens that mimic physiologic insulin secretion. Insulin regimens include multiple - component insulin regimens, multiple daily injections (MDIs), or continuous subcutaneous (SC) insulin infusion (CSII). Various newer forms of insulin available are Inhaled insulin Afrezza,

5. Emerging *biomarkers* are continually being researched to improve the early detection of cardiorenal complications in diabetes. Some newer biomarkers include:
   - *Cystatin C*: It is a marker of kidney function that can detect early changes in renal function more sensitively than traditional markers like creatinine. Elevated levels may indicate kidney dysfunction.
   - *Neutrophil Gelatinase-Associated Lipocalin (NGAL):* NGAL is an early marker of acute kidney injury and can help identify kidney problems at an earlier stage.
   - *Kidney Injury Molecule-1 (KIM-1)*: KIM-1 is another biomarker that indicates kidney injury and may be useful in detecting kidney damage in its early stages.

- *Fibroblast Growth Factor-23 (FGF-23)*: Elevated levels of FGF-23 have been associated with cardiovascular complications in diabetes, and it may serve as a predictor of cardiorenal risk.
- *Natriuretic Peptides:* Biomarkers like B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are conventionally associated with heart failure but may be helpful in identifying cardiorenal risk in diabetes.
- *Galectin-3*: Elevated levels of galectin-3 have been linked to fibrosis and cardiac remodeling and may be useful in assessing cardiac risk.
- *MicroRNA (miRNA):* Specific miRNAs in the blood have shown promise in identifying early signs of cardiorenal complications, as they can reflect changes in gene expression related to these condition.
- *Serum Mid regional ProAdrenomedullin (MR proADM*) also helps detect early cardiorenal dysfunction in diabetics.

6. *Digital Health and Telemedicine* - Wearable devices, and telemedicine for continuous monitoring and remote consultations, allow for real-time adjustments to treatment plans. Artificial Intelligence algorithms help to analyze patient data and provide personalized recommendations, predicting and preventing complications more effectively. It has been noticed that focusing on patient education and empowerment, involving individuals in decision-making and self-management enhances long-term adherence to treatment plans. Patient support networks are gaining importance where individuals with diabetes can share experiences and learn from one another.

7. *Regenerative Medicine* – There are ongoing studies which focus on stem cell-based treatments, to repair damaged pancreatic cells and potentially reverse diabetes. The field of Nutrigenomics is also being explored focusing on how an individual's genetic information can guide dietary choices, optimizing nutrition for better glycemic control and overall health.

8. *Genetic Markers*: Genetic markers like single-nucleotide polymorphisms (SNPs), DNA methylation, and microRNAs are associated with an increased risk of cardiorenal complications in diabetes. Newer markers are continually being identified, allowing for personalized risk assessment. Focus on mapping gut microbiota and its association with complication of diabetes is being studied extensively.

These biomarkers, when used in conjunction with clinical assessments and traditional markers, can provide a more comprehensive view of a patient's cardiorenal health. Early detection of complications is crucial for timely intervention and improved outcomes in individuals with diabetes.

Redefining strategies to prevent complications of diabetes requires a multidisciplinary and holistic approach, with a focus on personalized care, cutting-edge technologies, and proactive interventions. These innovations aim to improve the quality of life for individuals living with diabetes and reduce the burden of diabetes-related complications.