

A HOLISTIC STRATEGY OF DIABETES, A NEED OF THE HOUR

ABSTRACT

Increasing trend of global burden of diabetes mellitus and its complications involving cardiorenal systems due to lifestyle changes, ignoring the risk factors and late detection of complications like heart failure, atherosclerotic cardiovascular disease, renal failure poses an emergence to redefine strategies for early preventive management of complications and a need for a holistic approach of a disease. Diabetic prevention program (ADA guidelines 2023) involving lifestyle or behavioural intervention and in recent years, the introduction of newer drugs such as sodium-glucose cotransporter type 2 inhibitors, glucagon-like peptide-1 receptor agonist has shown benefits of prevention of complications with type 2 DM offering a new therapeutic opportunity, especially for cardiorenal patients, shown benefits in cardio vascular disease in addition to a reduced risk of CKD progression.⁽¹⁾

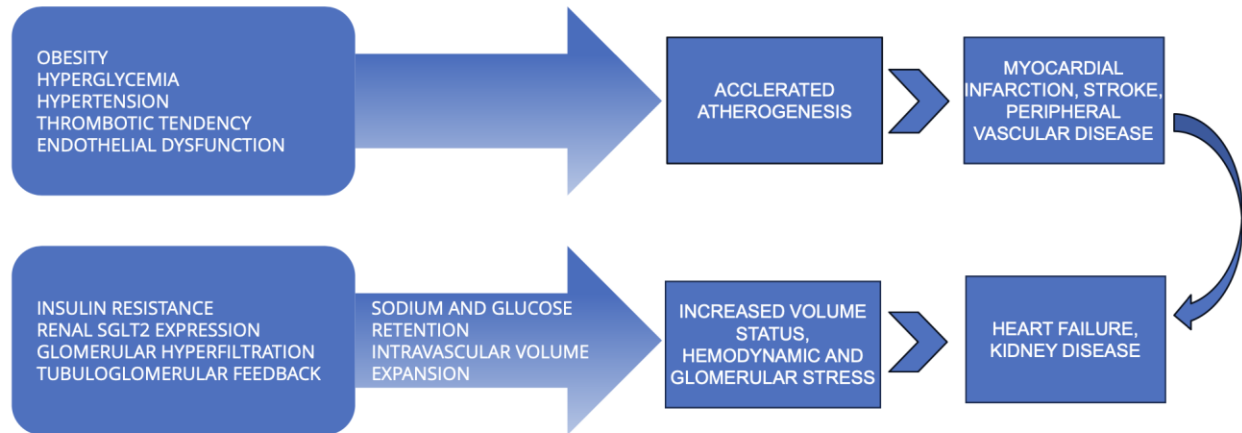
INTRODUCTION

Diabetes mellitus with its cardiorenal complications is associated with increased risk of hospitalization and mortality. The presence of cardiovascular risk factors, as well as the neurohormonal activation, inflammation and oxidative stress may be part of the pathophysiology. The complexity of these patients warrants a multidisciplinary approach.

Diabetic cardiomyopathy is the presence of a structurally and functionally abnormal myocardium in the absence of heart disease that justifies it in patients with DM. the role of hyperinsulinemia as a central key feature of how T2DM promotes heart failure by suppression of autophagy and promotion of oxidative stress and mitochondrial dysfunction, causing myocyte damage and activating sodium-hydrogen exchangers in cardiomyocytes and in the proximal renal tubules causing sodium retention and increased filling pressures. Also, epicardial adipose tissue expansion resulting in secretion of proinflammatory adipocytokines acting as a paracrine organ on the myocardium and causing microvascular dysfunction, inflammation and fibrosis. The predominance of cardiomyocyte death would lead towards a HFrEF phenotype and in contrast HFpEF would emerges in cases with prominent coronary microvascular endothelial inflammation with concentric left ventricle remodeling and higher stiffness.

In addition, risk factors linked to diabetes such as dyslipidemia or hypertension, obesity and insulin resistance also contribute to cardiorenal injury.

MECHANISM OF CARDIORENAL COMPLICATIONS IN DIABETES MELLITUS ALONG WITH ITS RISK FACTORS AND CO-EXISTING DISEASES ⁽²⁾



THE HOLISTIC APPROACH BY THE INTER PROVIDER 'COULD BE A FAMILY PHYSICIAN'

In the current dominating consultative model of care, ease of access to health services in networked systems has facilitated for more referrals but there is no centralisation of care associated with one physician or clinic, as patients may rotate between multiple providers (primary care practitioner, endocrinologist, cardiologist), with a considerable overlapping in management. This leads to interference in deciding the optimal drug class, dosing, drug interactions and may confuse patients receiving misaligned recommendations from multiple providers, resulting in ineffective follow-ups, and even eroding trust, especially when inter-provider communication is lacking.⁽²⁾

When it comes to DM and co-existing comorbidity management in a patient-centred fashion is vital. Other essential aspects of cardiometabolic therapy, such as lifestyle modification and psychological counselling, are inadequately addressed in the conventional model of care. Hence there is an urgent need of holistic approach strategy for all patients irrespective of the socioeconomic status through a healthcare inter-provider. A common inter-provider can be (primary care practitioner) Family physician or a General practitioner, should be the initial healthcare provider providing the patient with the single health record to maintain it with the initial evaluation including the lifestyle management to all the investigations reports, information of the referrals of specialists, follow up calendar etc.

Recently, many cardiovascular outcome trials (CVOTs) evidence calls for practice recommendations to help clinicians manage patients with complex conditions involving diabetes, cardiorenal, and/or metabolic (DCRM) diseases. The ultimate goal for these recommendations is

to be comprehensive yet succinct and easy to follow by the nonexpert whether a specialist or a primary care clinician. The recommendations are presented as 18 separate graphics covering lifestyle therapy, patient self-management education, technology for DCRM management, prediabetes, cognitive dysfunction, vaccinations, clinical tests, lipids, hypertension, anticoagulation and antiplatelet therapy, antihyperglycemic therapy, hypoglycemia, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), Atherosclerotic cardiovascular disease, heart failure, chronic kidney disease and comorbid heart failure and chronic kidney disease as well as a graphical summary of medications used for DCRM. ⁽³⁾

EARLIER THE CHANGE, LATER THE COMPLICATIONS; THE DIABETES PREVENTION PROGRAM (DPP) ⁽²⁾

The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study, 43% reduction at 7 years in the Finnish DPS, and 34% reduction at 10 years and 27% reduction at 15 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min moderate-intensity physical activity per week, such as brisk walking. Although weight loss was the most important factor in reducing the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44%.

Nutrition counseling for weight loss in the Diabetes Prevention Programme (DPP) lifestyle intervention arm included a reduction of total dietary fat and calories. Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes. Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes.

PHARMACOLOGIC INTERVENTIONS ⁽²⁾ FOR PREVENTION

Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program, especially those aged 25–59 years with BMI ≥ 35 kg/m², higher fasting plasma glucose (e.g., ≥ 110 mg/dL), and higher A1C (e.g., $\geq 6.0\%$), and in individuals with prior gestational diabetes mellitus. A Long-

term use of metformin may be associated with biochemical vitamin B12 deficiency so periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy is necessary.

NEWER PHARMACOLOGICAL DRUGS IN PREVENTION OF PROGRESSION OF CARDIORENAL COMPLICATIONS

New classes of antidiabetic agents, like SGLT2is and GLP-1 RAs, have shown a significant reduction in cardiovascular and renal outcomes in patients with T2DM and CKD. These drugs have revolutionized the management of patients with diabetic CKD with high risk for cardiovascular events, independent of glycemic control. ⁽¹⁾

The mechanisms that explain the effects of SGLT2is on HF outcomes and progression of kidney disease are possibly multifactorial. SGLT2is produce natriuresis, reduce volume overload and have direct hemodynamic effects by decreasing glomerular hyperfiltration. Moreover, SGLT2is are associated with reduced inflammation and oxidative stress, improved cardiovascular efficiency, blood pressure control, and weight loss, which are factors linked to HF outcomes. SGLT2is act by inhibiting SGLT2 expressed in proximal convoluted tubule (PCT) lowering glucose reabsorption. This increase of glucose excretion results in better glycemic control. ⁽¹⁾

Cardiovascular benefits associated with GLP-1 are multiple. It is known that inflammation play an important role in atherosclerosis development. GLP-1 in different studies reduce endothelial dysfunction and inflammation which can decrease the risk and progression of atherosclerotic plaque. Moreover, it has been described an improvement in lipid metabolism and reduction in blood pressure due to natriuretic effects. These mechanisms can act synergistically improving the cardiovascular profile of the diabetic patient. ⁽¹⁾

The non-steroidal MRAs such as finerenone have shown effects as potent as spironolactone and a higher selectivity when compared to eplerenone. The FIDELITY study combined the results of the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD RCT. In the pooled analysis of 13,026 patients treated with finerenone or placebo and followed for a median of 3 years, there was evidence of a 23% reduction in the relative risk of developing a sustained decline of $\geq 57\%$ from baseline in GFR or death due to renal causes. Additionally, finerenone provided a 14% reduction in the relative risk of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF, and the improvement in the composite cardiovascular outcome was due largely to a decrease in HF hospitalizations. ⁽¹⁾

Endothelin receptor antagonists prevent endothelin's deleterious effects, being endothelin receptor A (ETA) the receptor most frequently involved in the negative effects of the endothelin pathway (vasoconstriction, endothelial injury, or podocyte injury). Thus, endothelin receptor blockade has been traditionally directed to ETA blockade. ETA antagonism has shown renal protective effects, but fluid overload caused by the blockade of the ETA-mediated natriuretic effects has been an important limitation. In 2009 the ASCEND trial that included

T2DM patients that were treated with avosentan (ETA:B selectivity 50–300:1) was stopped prematurely after a higher incidence of fluid overload and heart failure events in the active-treatment arm. Nevertheless, avosentan showed a 30% median reduction in albuminuria compared to placebo. In order to avoid fluid retention, a more recent trial with atrasentan (ETA:B selectivity 1,200:1) randomized only responder patients (reduction of 30% in albuminuria without weight gain or increase in BNP) to receive active treatment or placebo. However, in the ETA antagonist group, fluid retention and anemia were more frequent. Recently, it has been hypothesized that the combination of SGLT2i and ERAs could have synergistic cardiorenal protective effects, as both drug classes act through different pathways, and SGLT2i could prevent the fluid overload and anemia linked to the use of ERAs. ⁽¹⁾

The soluble guanylate cyclase (sGC) stimulator is a drug class more recently studied in RCT. Endothelial nitric oxide (NO) has cardiovascular protective effects, including vasodilation, reduction of vascular oxidative stress, improved diastolic relaxation, and inhibition of fibrosis and smooth muscle cell proliferation. A RCT evaluating treatment with vericiguat (an oral sGC stimulator) in patients with HFrEF that included 46.9% patients with diabetes showed a reduction of the primary CV composite outcome after a median follow-up of almost 11 months. The reduction was mainly due to a decrease in hospitalization for HF. ⁽¹⁾

CONCLUSION

In conclusion, the increasing global burden of diabetes mellitus and its associated complications, particularly cardiorenal issues, demands a holistic strategy for prevention and management. The complexities of diabetes-related cardiomyopathy, heart failure, and kidney disease require a multidisciplinary approach, involving cardiologists, nephrologists, endocrinologists, and primary care physicians.

Emerging pharmacological options like sodium-glucose cotransporter type 2 inhibitors, glucagon-like peptide-1 receptor agonists, non-steroidal MRAs like finerenone, and novel agents like tirzepatide and selective endothelin receptor antagonists show promise in preventing and managing diabetic complications, especially in cardiorenal aspects. These drugs offer improved cardiovascular outcomes, renal protection, and potential synergistic effects when used in combination.

In summary, a holistic approach to diabetes care, encompassing lifestyle modifications and the judicious use of pharmacological interventions, is crucial in addressing the growing global diabetes epidemic and its associated cardiorenal complications. Collaboration amongst healthcare providers from various specialties is essential to optimize patient outcomes and improve the overall management of this challenging disease.

REFERENCES

- (1) <https://www.frontiersin.org/articles/10.3389/fcvm.2023.1185707/full#:~:text=CRS%20is%20a%20bidirectional%20relationship,quality%20of%20life%20of%20patients>
- (2) https://diabetesjournals.org/care/article/46/Supplement_1/S5/148048/Summary-of-Revisions-Standards-of-Care-in-Diabetes
- (3) <https://www.sciencedirect.com/science/article/pii/S1056872721003251>