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Systemic effects of type 2 diabetes therapies: an integrated perspective on the cardio–renal–cerebral–metabolic axis

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Type 2 diabetes (T2D) has been treated as an underlying disease—hyperglycemia, but is instead a systemic disease—mediating the network of neural, endocrine, and immune signaling. In recent years, the concept of the cardio–renal–cerebral–metabolic axis has provided an integrative pathophysiological framework for understanding the multisystem complications of diabetes. From this perspective, the present review systematically elucidates the substantial evolution in modern T2D therapeutic strategies from simple glycemic control to comprehensive multi-organ protection. The primary pathology is that high insulin resistance and chronic metabolic disturbances trigger oxidative stress and inflammation, which in turn drive a vicious cycle in the heart, kidneys, and brain. In this review, we demonstrate that new drugs based on sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and mineralocorticoid receptor antagonists, which are capable of lowering glucose to promote efficient glycemic control, decrease cardiovascular events, lower the risk of renal disease, and demonstrate neuroprotective properties as the key to organ protection. Additionally, non-pharmacological interventions and new treatments can be combined as a multi-targeting, multilayer management system. Furthermore, greater knowledge and integration of the cardio–renal–cerebral–metabolic axis could signal a shift toward precision medicine to stabilize the network's homeostasis and improve long-term patient outcomes.

KEYWORDS

cardio–renal–cerebral–metabolic axis, chronic inflammation, organ protection, precision medicine, type 2 diabetes

1 Introduction

1.1 Overview of type 2 diabetes

A significant characteristic of type 2 diabetes is the interaction of insulin resistance with beta-cell dysfunction (1, 2). We start with impaired glucose uptake as peripheral tissue becomes less sensitive to glucose, and gradually decrease the effectiveness of the bio-cell compensatory function (3–6). Chronic inflammation and oxidative stress due to metabolic fluctuations are key links, including mitochondrial dysfunction, which leads to multi-organ injury (1, 4).

T2D is a worldwide health burden for 90%–95% of all diabetes cases and tens of millions of people worldwide. It remains one of the leading causes of death in low-income countries and among younger people (7–12). A recent GBD study corroborates that the disability-adjusted life years (DALYs) for T2D increased from around 27.4% in 1990 to 2021 (13, 14). Low- and middle-income Countries (LMICs) have been heavily affected due to rapid urbanization and lifestyle changes (13). High body mass index (BMI) remains the major risk factor for 52.2% of T2D-related DALY in 2021, 24.3% higher than in 1990 (15). Disease burden increases among those under 20 years of age: there were 128.7 and 439.9% of people under 20 years old between 1990 and 2021 (16). T2DT and hyperglycemia in China resulted in 0.9 million deaths and 26.8 million DALYs in 2021 (three times those of 1990), and are expected to be 18.17% by 2050 (16). Taken together, these results underscore the acceleration and the more youthful global burden of T3D due to obesity, which remain largely unknown (15, 16).

This disease is systemic, and we conclude that T2D is not merely a disease of glucose regulation but one caused by genetic, environmental, and lifestyle factors that affect multiple organs, such as the heart, kidneys, and brain (17, 18). The severe consequences of T2D include severe multisystem problems: dyslipidemia-induced risk of heart attack and stroke, diabetic death from kidney failure, and neurological disorders that share pathological mechanisms with Alzheimer's disease and increase patient disability and death (19, 20).

In summary, the core pathophysiological process of T2D manifests as progressive metabolic dysregulation and represents a complex network disorder characterized by multisystem interactions (17). Despite the global spread of risk factors that aggravate the disease burden, there is still a lack of effective early predictive biomarkers and individualized therapeutic tools (9, 18). Traditional models view problems as one-to-one or only include dual-organ interactions (e.g., cardio-renal). However, they fail to capture the overall influence of metabolic drivers on the brain and feedback loops. In recent years, researchers have proposed the idea of a cardio-renal-cerebral-metabolic axis to describe the molecular and physiological mechanisms underlying the multisystem dysfunction associated with diabetes, as a model for implementing therapeutic plans. Understanding the physiological and pathological interactions of cardio-Renal-Cerebral-metabolic, therefore, is a prerequisite for developing global systemic approaches.

1.2 The cardio–renal–cerebral–metabolic axis: an integrative pathophysiological model

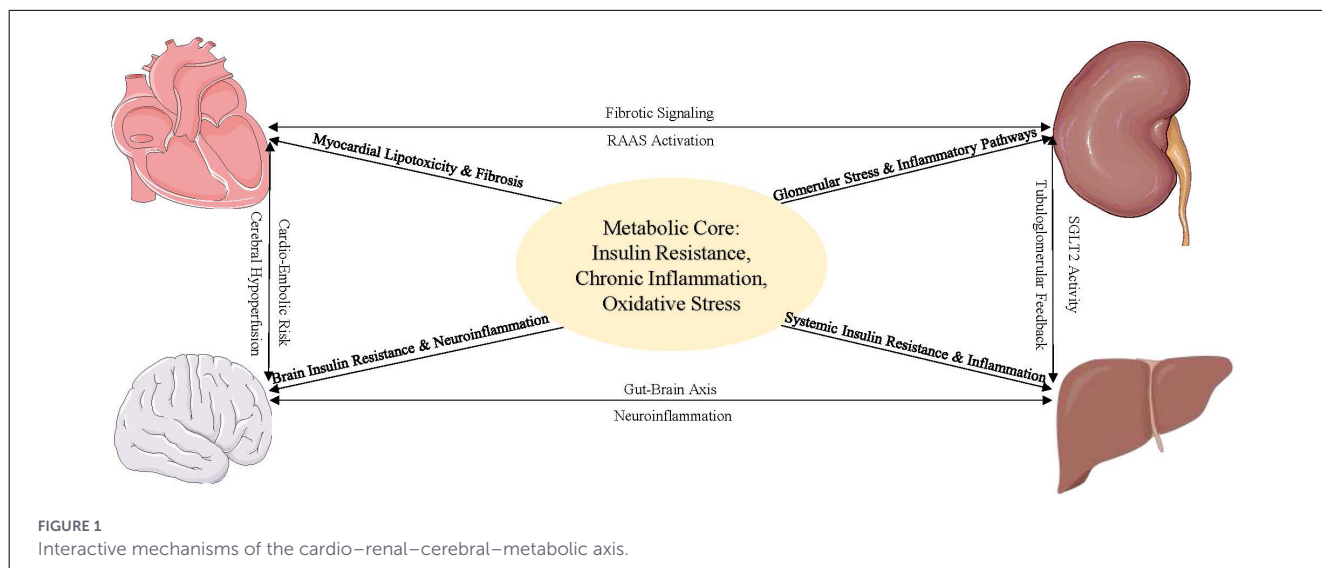
The cardio-renal-cerebral-metabolic axis describes a multi-system network of interactions among the heart, kidneys, brain, and metabolic system via neural, endocrine, and metabolic signals. For diabetes, it highlights that glycemic control, cardiorenal function, and cognitive abilities are tightly coupled: If any part of this system fails, it triggers cascading effects that result in the coordinated deterioration of multiple organs and ultimately worsen patients' outcomes (21–24).

The proposed framework is conceptually distinct from existing multi-organ models. While the traditional Cardio-Renal Syndrome primarily focuses on hemodynamic cross-talk, and the Gut-Brain Axis emphasizes satiety signaling, these frameworks often fail to capture the systemic nature of metabolic comorbidities (25–27). In contrast, the Cardio-Renal-Cerebral-Metabolic Axis integrates these systems by positioning “Metabolic Dysregulation”—specifically chronic inflammation and insulin resistance—as the central upstream driver connecting the heart, kidneys, and brain, rather than merely hemodynamic consequences (28, 29). Recent evidence underscores that traditional models overlook the profound neurocognitive impact, where metabolic abnormalities directly impair blood-brain barrier integrity and synaptic function, leading to a two- to four-fold increase in cognitive impairment risk independent of vascular events (30–32). Clinically, this distinction justifies a paradigm shift from reactive management of dual-organ failure to proactive, holistic protection that targets these shared metabolic roots.

Rather than competing dual-organ schemes, the new model allows the brain to serve as the regulator, regulating metabolic functioning as a daily system. This would require therapy from shielding individual organs to repairing the whole system. The metabolic issues of diabetes (insulin resistance, inflammation) pose a double challenge; they damage cardiorenal integrity and, through pathways (e.g., gut-brain axis), reach the hippocampus, and make us cognitively impaired (33–37). Conversely, deterioration in brain regulatory functions, such as impaired neural plasticity, can weaken patients' capacity for disease self-management, creating a vicious cycle that further disrupts metabolic homeostasis (38–41).

Diabetes-induced myocardial dysfunction and heart rate variability may have both a serious risk and an underlying cause, vascular dysfunction of the kidneys, which drives one another, and leads to a cycle of concurrent cardiorenal decline (42, 43). The kidneys regulate the metabolic system by maintaining fluid balance and excreting glucose. If the kidneys are injured, it can activate the hypothalamic–pituitary–adrenal axis, which can worsen systemic metabolic dysregulation (44, 45). In terms of the brain, gut microbiota and associated hormones regulate glucose and lipid metabolism and interact with cognition via vagal pathways and metabolic abnormalities, e.g., hyperglycemia, which affect hippocampal metabolites as markers of cognitive dysfunction (23, 46). The metabolic system is the primary mediator of inter-organ damage when glucose and lipid metabolism cause oxidative stress and inflammation (22, 46).

Overall, the complexity of the cardio–renal–cerebral–metabolic axis underscores the need for integrated interventions that may provide a unified model of the multisystem complications of diabetes and a global perspective on this complex pathophysiological network. The essential mechanisms are summarized in Figure 1. The perspective for future treatment is to move from an individual-organization or signaling pathway approach to system-level approaches to restore network homeostasis (47, 48). Based on this systematic approach, the subsequent sections will discuss how therapies are evolving to target these nodes.



2 Major therapeutic strategies for type 2 diabetes

2.1 Pharmacological strategies: the evolution from glucose lowering to organ protection

Beyond the proposed switch to the cardio-renal-cerebral-metabolic axis, T2D has achieved a dramatic transition from simple glucose control to organ protection with therapeutic goals that no longer restricted to glycemic target, but toward systemic interventions that delay metabolic damage to heart, kidneys, and brain. This has been motivated by strong evidence in many large cardiovascular outcome trials, namely that certain new antidiabetic drugs can reduce the risks of heart failure, kidney disease progression and death while keeping glycemic control (26, 49). On this basis, the cardio-renal-cerebral-metabolic axis is based on the theory of such an integrated management strategy (50).

Among traditional medications, the United Kingdom Prospective Diabetes Study (UKPDS) proposed metformin as the first-line primary therapy because it improves the insulin sensitivity by activating the AMPK pathway (51). While older hypoglycemic agents can provide glucose lowering functions, they cannot offer long-term safety and organ-preserving benefits (52, 53). To clarify their role within the axis model, the individual organ effects and potential risks of the classical agents (Sulfonylureas, Thiazolidinediones, DPP-4 inhibitors, Insulin) are summarized in Table 1. Even though they work well in glycemic control, their unrepresentative cardiorenal benefit is far from being identical to new therapies. This highlights the inadequacy of a purely “glucose-centered” treatment model and motivates the development of novel agents with distinct organ mechanisms (54).

The new therapeutic approach has been demonstrated by recent studies conducted between 2023 and 2025. The FLOW trial provided the study on GLP-1 receptor agonists, showing that semaglutide reduced the risk of major kidney disease events by 22% (HR: 0.78) in CKD patients, irrespective of baseline use

(55, 56). In terms of cardiovascular and metabolic integration, the SELECT study showed that semaglutone reduced major adverse cardiovascular events (MACE) by 20% in overweight and obese patients while even without diabetes, suggesting the importance of targeting upstream metabolic drivers (57, 58). EMPEROR-Preserved and DELIVER presented evidence of the role of SGLT2 inhibitor in heart failure with preserving ejection fraction (HFpEF) in which there are still significant reductions in cardiovascular death or heart failure hospitalization by about 21% (59, 60). Finally, recent dual GIP/GLP-1 receptor agonist SURPASS showed superior potential, suggesting 27% reduction in MACE and significant improvement in renal endpoints compared to insulin glargine (61, 62). All these studies corroborated a shift toward a systematic cardio-renal-cerebral-metabolic management model.

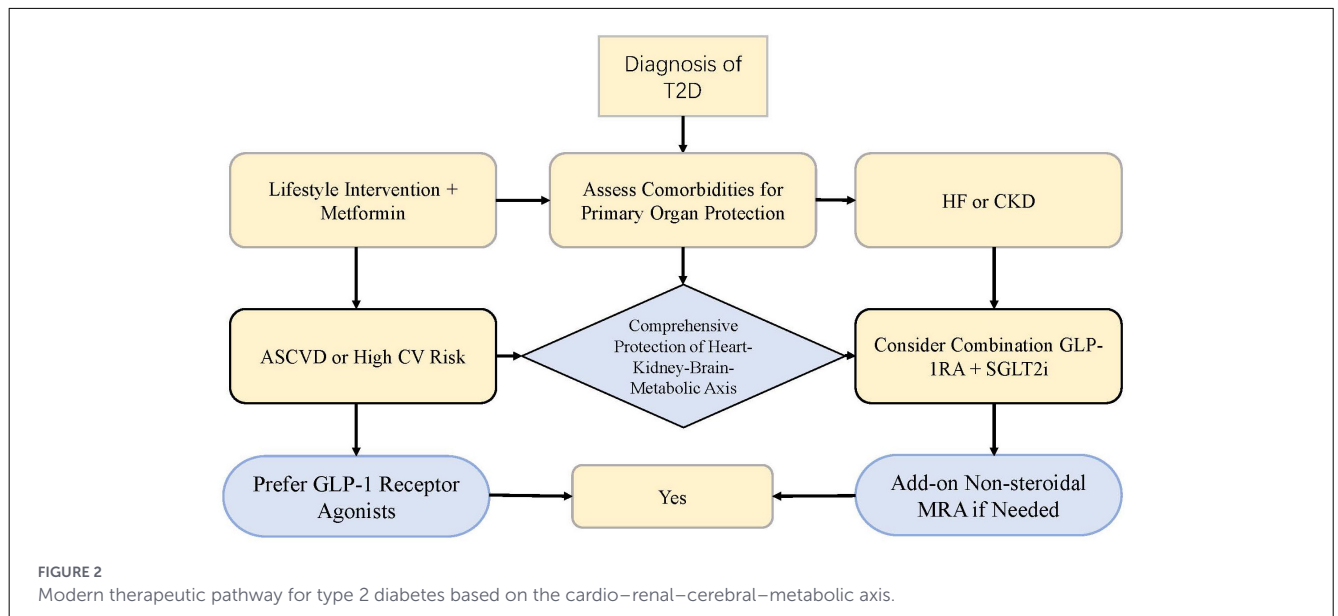
This new generation sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are the key players in interventions targeting the cardio-renal-cerebral-metabolic regime. The key components of their development, and most importantly their physiological functions, are their molecular functions. The SGLT 2 inhibitors repress the glucose and sodium uptake in the proximal tubule, inducing osmotic diuretic respiration and natriuresis. This facilitates the suppression of blood glucose, decreases the heart preload/afterload, and shifts the metabolic substrate consumption toward ketones (63–65). GLP-1 receptors suppress the secretion of insulin, slow down gastric digestion and reduce appetite to bring heavy losses and have anti-inflammatory and anti-atherosclerotic effects of improving the endothelial function and oxidative stress markers (66, 67).

Based on these mechanisms, modern T2D management has become a structured mechanism as illustrated in Figure 2. It starts with T2D diagnosis, and lifestyle change plus metformin is initiated. One can take into account comorbidities to decide which organ-protective drugs should be used: for atherosclerotic cardiovascular disease (ASCVD), or high cardiovascular risk, GLP-1 receptor agonists should be preferred; for heart failure (HF) or chronic kidney disease (CKD), SGLT2 inhibitors should be

TABLE 1 Positioning of traditional glucose-lowering agents within the cardio–renal–cerebral–metabolic axis.

Drug class	Cardiovascular impact	Renal impact	Neuro-cognitive impact	Metabolic profile and key risks
Metformin	Neutral/potential benefit	Neutral	Potential benefit	Weight neutral
	Evidence suggests reduced risk of MI (UKPDS), though less robust than novel agents (e.g., SGLT2i/GLP-1 RA).	No direct nephroprotection beyond glycemic control; dose adjustment required based on eGFR.	Observational data link use to lower dementia risk; crosses the blood-brain barrier.	Risks: Vitamin B12 deficiency; lactic acidosis.
Sulfonylureas	Neutral	Neutral	Potential risk	Weight gain
	Cardiovascular safety is generally established, but lacks the specific protective benefits seen in newer classes.	No specific protective effects; requires dose adjustment in CKD.	Severe hypoglycemia events is strongly associated with increased risk of cognitive decline.	Risks: Severe hypoglycemia (dangerous for the elderly).
Thiazolidinediones	Mixed profile	Neutral	Potential benefit	Weight gain
	Reduces risk of stroke and MI, but carries a high risk of fluid retention and hospitalization for heart failure.	No significant impact on CKD progression beyond glycemic control.	Reduced recurrent stroke risk; potential insulin-sensitizing effects in the brain.	Risks: Fluid retention, edema, bone fractures, heart failure.
DPP-4 inhibitors	Neutral	Neutral	Neutral	Weight neutral
	Proven cardiovascular safety but no reduction in MACE or heart failure risks.	Safe in renal insufficiency; may significantly reduce albuminuria levels.	No consistent evidence of neuroprotection or cognitive harm.	Risks: Joint pain; Pancreatitis (rare).
Insulin	Neutral	Neutral	Indirect risk	Weight gain
	Effective for glycemic control; neutral for cardiovascular outcomes (ORIGIN trial).	Safe in advanced CKD; essential for preventing microvascular damage via glucose control.	Peripheral hyperinsulinemia does not equal central effect; hypoglycemia poses direct cognitive risks.	Risks: Hypoglycemia; Injection site reactions.

CV, cardiovascular; BBB, blood-brain barrier; CKD, chronic kidney disease; HF, heart failure; MI, myocardial infarction; MACE, major adverse cardiovascular events.



recommended. For patients with complex diseases, or a greater level of protection, GLP-1 receptor antagonists should be considered as a combination of GLP-1 receptor inhibitors and SGLT2 inhibitors to obtain their enhanced cardiorenal benefits. In patients

with high risk of disease such as T2D and CKD, a nonsteroidal mineralocorticoid receptor antagonist may also provide additional cardiorenal benefits. Overall, modern T2D treatment for T2 is composed by SGLT2 inhibitors, GLP-1 receptor antagonist

and mineralocorticoid receptor antagonist (MRA) to go from “glucose lowering alone” to “systemic multi-organ protection and comorbidity-based precision treatment pathways” (26, 68). However, pharmacological therapy is insufficient to address the metabolic dysregulation completely and including non-pharmacological and emerging therapies has been one of the key approaches to T2D management.

2.2 Non-pharmacological therapy

Non-pharmacological measures in controlling T2D in general work in synergy with the pharmacological measures to form the basis of disease management. Dietary and exercise measure insulin sensitivity, inflammatory response, and influence gut microbiota-based metabolites to allow for a long-term success of the clinical treatment from the metabolic point of view. Diet control: Healthy eating patterns such as high-fiber or Mediterranean diets can significantly improve glycemic homeostasis and reduce cardiovascular risk (69–71). Exercise not only maintains glycemic stability, but it is also effective against microvascular complications as an physiological anti-inflammatory strategy to maximize metabolic function (72, 73). Weight management is of primary use for obesity patients: evidence based weight reduction can be beneficial in terms of metabolic control; paired with structured lifestyle interventions, it might even result in disease recovery (74, 75). Furthermore, we demonstrated that changing the disease process could yield promising results in recent studies. For example, the DiRECT study showed that intensive weight control in primary care could lead to remission of 46% of patients within 1 year, which strongly rejects the idea of T2D as a gradual disease (76–78). Regarding long-term morbidity, though Look AHEAD found that lifestyle intervention may not be a major success in terms of major cardiovascular events, it clearly has multiple benefits for patients’ survival. For example, this intervention was effective in secondary outcomes, including preventing obstructive sleep apnea and improving physical activity, which reinforces the importance of non-pharmacological treatments for individual patients (78–80). In that case, systematic non-pharmacological treatments can be clinically useful to slow down disease development and to make long term effects (81).

2.3 Emerging therapies

While cell treatments for T2D have been investigated, other cell- and gene-based therapies have promising future therapeutic potentials for stabilizing the cardio-renal-cerebral-metabolic axis. With cell therapy, mesenchymal stem cell (MSC) transplantation (due to its multi-directional differentiation and unique immunomodulatory features) could potentially promote pancreatic β -cell regeneration and repair damaged islet tissue (82, 83). Recent evidence highlights their systemic value beyond the pancreas: MSC-derived exosomes can deliver miRNAs to inhibit fibrosis and inflammation in the kidneys and heart, and potentially exert neuroprotective effects by modulating neuroinflammation, offering a “multi-organ repair” mechanism

(84–86). Gene therapy aims at correcting metabolic pathway abnormalities at the root of the disease. Applications like the CRISPR/Cas9 genome-editing systems and GLP-1 gene delivery vectors have opened new opportunities for precise control of pathogenic genes (87–91). Specifically, these approaches can ensure continuous endogenous GLP-1 production, providing stable metabolic homeostasis superior to the fluctuations seen with daily pharmacotherapy (82, 92).

These new technologies have safety challenges, such as the impaired survival of MSCs in high-glucose environments and the immunogenicity of viral vectors (89, 93). Long-term stability, and ethical control remain prerequisites, but these innovations have provided a foundation for the future of systemic diabetes treatment (87, 94).

3 Effects of type 2 diabetes treatment on the heart

3.1 Association between diabetes and cardiovascular disease

Studies show that T2D is also an independent risk factor for heart disease. Large cohort data show that patients with T2d risk both coronary artery disease and heart failure, with patients being over four times more likely to develop coronary disease than non-diabetic patients (95, 96). Remarkably, even without overt coronary artery disease, T2D itself can also result in structural and functional abnormalities of the myocardium, a different clinical type that is called diabetic cardiomyopathy (97–99).

The key mechanisms of pathogenesis include multiple damages due to chronic hyperglycemia, insulin resistance and lipid metabolism: metabolic damage drives atherosclerosis via oxidative stress and endothelial disorders (100, 101); chronic inflammation, accumulation of advanced glycation end products (AGEs), and myocardial energy metabolic remodeling—characterized by impaired glucose utilization and excessive fatty acid oxidation—directly damage cardiomyocytes and induce fibrosis and apoptosis (102, 103); concurrently, characteristic coronary microcirculatory dysfunction further exacerbates myocardial ischemia and contractile impairment (104). Collectively, these factors lead to diabetic cardiomyopathy, which is characterized by early diastolic dysfunction and slow systolic degradation which becomes apparent even in absence of coronary artery lesions (105, 106). This condition carries critical clinical significance.

3.2 Cardioprotective effects and mechanisms of type 2 diabetes therapeutic agents

T2D patients are more than two times more likely to die from atherosclerotic death from heart disease than non-diabetic patients (100, 107, 108). Diabetes myocardial changes: metabolic defects, microcirculatory dysfunction and interstitial fibrosis, which all lead to progressive changes in the diastolic

and systolic function (109). In order to track these disorders, based on the systemic strategies introduced in Section 2.1, clinical trials show significant organ-related benefits. For SGLT-2i, large-scale cardiovascular outcome trials (CVOTs) have always proven effective in reducing heart failure risk. Recent updates from EMPEROR-Preserved and DELIVER have expanded this benefit to patients with HFpEF, reducing the composite risk of cardiovascular death or hospitalization by 21% (59). The data show that SGLT-2i reduces mortality of the heart by about 30% and heart failure hospitalization by 35%, respectively. Results show SGLT-2i can reduce cardiovascular death by around 30% and heart failure hospitalization by 35% (50, 109–111). All the benefits of heart-specific hemodynamic optimization include reducing the stress of the ventricular wall and preventing the heart-frosis (112). On the other hand, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are more favorable for major adverse cardiovascular events by 12%–14% and non-fatal stroke (50, 109). These protective factors rely primarily on anti-atherosclerotic actions, such as plaque stabilization and improvements of coronary microvascular functioning (66). Nonsteroidal MRAs such as finerenone block mineralocorticoid receptors, reducing myocardial inflammation and fibrosis, and slowing down ventricular hypertrophy and diastolic dysfunction (50, 113). Collectively, such agents are central to cardioprotection, with SGLT-2i focusing on heart failure and GLP-1 targeting ischemic events. Effects of Type 2 Diabetes Treatment on the Kidneys.

3.3 Pathophysiological mechanisms of diabetic kidney disease

The main mechanism underlying diabetic kidney disease (DKD) in T2D stems from chronic hyperglycemia-induced metabolic dysregulation and multiple signaling abnormalities. Hyperglycemics promote increasing production of higher glycation end products (AGEs), activate receptor AGEs and produce more than abundant mitochondrial ROS production, directly damaging glomerular endothelial cells, podocytes and tubular epithelial cells (114–116). Glomerular remodeling and impaired tubuloglomerular feedback, leading to intraglomerular hypertension and hyperfiltration of kidney tissues, and a persistent increase in kidney function. In addition, the hyperglycemic environment keeps increasing and increasing the proliferation of various profibrotic and proinflammatory pathways: TGF- β promotes extracellular matrix accumulation and glomerulosclerosis and tubulointerstitial fibrosis; PKC promotes ROS production by NADPH oxidase activation and oxidative damage; NF- κ B promotes proinflammatory cytokine releases, such as TNF- α and IL-1 β , and cooperating with the NLRP3 inflammasome, which leads to local renal inflammation (114, 117–120). These interconnected processes form a vicious cycle of “oxidative stress–inflammation–fibrosis,” which constitutes the central mechanism underlying the progression of DKD (119, 121). Notably, renal impairment further activates neuroendocrine feedback systems—particularly the renin–angiotensin–aldosterone system (RAAS)—thereby

aggravating cardiac load and contributing to the “cardio–renal vicious cycle.”

3.4 Renoprotective effects and mechanisms of type 2 diabetes therapeutic agents

As one of the most severe microvascular complications of T2D, diabetic kidney disease is a major cause of end-stage renal disease (ESRD) (122, 123). The novel drugs in turn can translate these systemic drugs into renal benefits, which result in a great success in delaying disease progression. For SGLT-2i, the primary renal-related benefit is from restoring tubuloglomerular feedback, which decreases intraglomerular pressure and filtration (124). Clinical trials have established that SGLT-2i greatly slows down estimated glomerular filtration rate (eGFR) and decreases the risk of ESRD with no glycemic control (122, 125). For GLP-1 RAs there has been evidence that the urinary albumin-to-creatinine ratio (UACR) and glomerular permeability were greatly reduced due to local anti-inflammatory processes and endothelial integrity (111). In addition nonsteroidal MRAs (e.g., finerenone) were found to slow down CKD progression and decrease ESRD incidence by suppressing inflammation and fibrosis within the renal interstitium (126). These results show a shift in nephrology from reactive management to proactive immunization of the kidney.

4 Effects of type 2 diabetes treatment on the kidneys

4.1 Type 2 diabetes and cognitive impairment: from metabolic dysregulation to brain injury

The epidemiological evidence for T2D is that it is a risk factor for cognitive decline, vascular dementia, and Alzheimer’s disease. The pathogenesis is far from only metabolic and neurodegenerative features such as insulin signaling dysregulation, oxidative stress, and neuroinflammation. There are common “metabolic–neuronal injury” processes in the literature (127). At the medical level, several processes play important roles: neuronal insulin resistance leads to poor glucose use, leading to impaired synaptic plasticity of major regions such as hippocampus. *In vivo*, abnormal hippocampus N-acetylaspartate/creatinine (NAA/Cr) ratios are observed in T2D patients, providing *in vivo* evidence of neuronal metabolic dysfunction and apoptosis. In parallel, persistent hyperglycemia leads to microvascular endothelial dysfunction and high BBB permeability by creating white matter lesions and localized ischemia due to small extracellular vesicle-induced vascular injury. Chronic inflammation and oxidative stress are also contributing to inflammation and reactive oxygen species (ROS) activation by triggering microglia triggering a neuroinflammatory process affecting BBB integrity (128, 129). These processes, coupled with inflammation and oxidative stress, are critical factors of neuronal injury in the cardio–renal–cerebral network.

Recent studies show that the level of cognitive impairment positively correlates with diabetes duration, glycemic variability and insulin resistance (130, 131). In general, our results indicate that T2D-associated cognitive dysfunction can be interpreted as a multi-target injury of the “vascular–neuronal–glial network” due to metabolic disruption.

4.2 Neuroprotective potential of type 2 diabetes therapeutic agents

In recent years, novel antidiabetic agents such as GLP-1 RAs have demonstrated significant neuroprotective potential beyond glycemic control (132, 133). Mechanically, such benefits are mediated by direct and indirect processes. For direct central processes, it has been previously established that GLP-1 RAs may enter the blood-brain barrier to activate certain receptors widely expressed in the hippocampus and cortex, stimulate BDNF expression and improves synaptic plasticity, and inhibiting microglial activation to reduce brain inflammation and reduce Alzheimer’s pathology (e.g., β -amyloid deposition and Tau hyperphosphorylation). For indirect systemic mechanisms, these agents protect the brain by optimizing glycemic and lipid control, reducing systemic chronic inflammation and oxidative stress, and promoting endothelial functioning to prevent neurovascular injury and maintain blood-front barrier integrity (134, 135). The clinical results show that GLP-1 RAs, such as liraglutide, semaglutin, improve cognitive function in Alzheimer’s disease animal models and prevent dopaminergic neuronal degeneration in Parkinson’s disease models (134, 136). However, it is strictly necessary to differentiate that animal models are supported by the regenerative effects of the regenerations, however human evidence is mostly supported by secondary studies of cardiovascular outcome trials and observational studies. Further randomized controlled trials, in particular, of cognitive outcomes, are still ongoing and necessary to confirm these neuroprotective effects.

SGLT-2i indirectly helps to maintain brain function through peripheral mechanisms through lowering blood glucose, reducing inflammation and oxidative stress, and improving heart, kidney and brain perfusion for a good system of the central nervous system (137). Observational studies indicate that SGLT-2i use is associated with a lower risk of Alzheimer’s disease ($HR \leq 0.67$) and slower cognitive decline, potentially related to reduced cardiovascular events (50, 109). Note that this neuroprotective effect of SGLT-2i does not provide evidence for the central mechanisms due mainly to the optimisation of systemic metabolic status. Importantly, current clinical data of SGLT-2i are observational, and significant evidence from cognitive-related RCTs are sparse. In general, GLP-1 RAs and SGLT-2i are promising but there remains a major gap between current evidence from CVOTs and current neurocognitive data, which is based on observational data. For these real-world data, however, certain biases, such as the “healthy user effect” or reverse causality, are dominant. Therefore, these agents are currently a “neuroprotective option” than existing cognitive therapy and must be confirmed through dedicated RCT with the main cognitive endpoints (138, 139).

5 Regulation of metabolism by type 2 diabetes treatment

5.1 Metabolic dysregulation: the common upstream driver of multi-organ injury

T2D is an intrinsically multiorgan disease. The fundamental pathology such as insulin resistance, lipid metabolic abnormality and hyperuricemia not only occur, but also share common pathogenic mechanisms that cause severe losses in the heart, kidneys, and brain (140, 141). In T2D patients, skeletal muscle and fat tissue are affected by high insulin signaling, lipid metabolism issues include high triglycerides and central obesity, as metabolic dysfunction associated steatotic liver disease (MASLD) and hyperuricemia contribute to this imbalance (28, 142–145).

These metabolic abnormalities cause systemic chronic inflammation, oxidative stress and endothelial dysfunction and are responsible for multi-organ functional decline: chronic low-grade inflammation and excessive ROS production caused by adipose tissue dysfunction directly affect vascular endothelium, kidneys, and neurons; insulin resistance coupled with hyperglycemia induce endothelial dysfunctions and microcirculatory dysfunction, which are early symptoms of atherosclerosis, nephropathy and neurodegeneration; ectopic lipid deposition causes mitochondrial dysfunction and endoplasmic reticulum stress, further impairing multi-organ cellular function (146–152). These pathological phenomena are a leading element of the cardio–renal–cerebral–metabolic axis; for instance, MASLD can also promote liver injury, heart failure, and cognitive decline through shared insulin resistance and inflammation with T2D and cardiovascular disease (29, 153–156). Thus, metabolic dysregulation is a comorbidity, and the main source of cross-organ injury. Appropriate metabolic responses such as insulin sensitivity, lipid disorders and inflammation and oxidative stress are essential for jointly protecting the heart, kidneys, and brain (28, 148, 155).

5.2 Metabolic modulation by therapeutic agents

T2D’s treatment goals have become more general than glycemic control to control systemic metabolic dysregulation, to improve glucose and lipid metabolism, insulin resistance and chronic inflammation in order to avoid cardiovascular and renal problems (157, 158). Metformin is a crucial ingredient in metabolic therapy. Metformin activates AMPK signaling to inhibit hepatic gluconeogenesis, increase peripheral insulin tolerance, and achieve mild weight loss and lipid control, which will be the basis of future multi-target metabolic management (159, 160).

To build upon this, GLP-1 RAs have large metabolic benefits: they can lower the weight by reducing the central appetite and slow gastric emptying, and lipid metabolism through lowering the serum triglycerides and high-density lipoprotein (22, 161). These agents alleviate hepatic steatosis by regulating gluconeogenesis and inflammation through adipose tissue–derived miRNAs, both enhancing insulin signaling (67). SGLT-2i achieve their own metabolic modulations by stimulating urinary glucose

and sodium uptake, increasing fatty acid oxidation, moderately losing weight, and reducing systolic blood pressure and serum uric acid concentrations (161). Their metabolic benefits come from reducing their total energy burden, reduced visceral fat accumulation, and decreasing the proinflammatory cytokines (162). This multipathway metabolic remodeling provides an energetically useful system organ protection.

Together GLP-1 RAs and SGLT-2i have complementary metabolic effects: GLP-1 RAs enhance insulin production, SGLT-2s enhance urinary glucose clearance, and they both have additive effects on glycemic and lipid control, while being conducive to cardio-renal stability (163, 164). Collectively, metformin, GLP-1 RAs and SGLT-2i combine to adjust glucose and lipid metabolism and energy homeostasis from “glycemic control alone” to “systemic metabolic remodeling” (158, 165).

5.3 Multifaceted effects of treatment strategies

Current T2D management strategies are evolving from single-target interventions to systematic integration of multi-pathway regimens. Evidence indicates that monotherapy is often insufficient to halt disease progression; thus, regimens combining agents with complementary mechanisms—specifically SGLT-2i and GLP-1 RAs—have become mainstream for restructuring metabolic networks (164, 166). Biologically, this combination plays roles both in a two-fold way: GLP-1 RAs, besides glucose control, improve heart health and decrease renal risk through anti-atherosclerotic and central energy-balance mechanisms, SGLT-2i lower blood glucose and enhance hemodynamics via osmotic diuresis, which increases the heart load and indirectly prevents kidney function (149, 167). This mechanism, not only maximizes glycemic control, but also restores the stability of the cardio-renal-cerebral-metabolic axis with dual hemodynamic and metabolic modulation (168, 169).

Beyond the two drug combinations, new therapies are focusing on unimolecular multi-receptor agonists which are more closely complementary. These multi-pronged treatments reduce systemic inflammation, improve insulin secretion, and promote metabolic homeostasis. They dramatically reduce oxidative stress and adipose tissue dysfunction (162, 170). By turning from simple add-on approaches to molecularly adapted approaches, this systematized approach can serve as the basis for precision medicine, finding individualized risk sources in order to significantly improve clinical performance and risk of complications (171, 172).

6 Integration and perspectives of the cardio-renal-cerebral-metabolic axis

The cardio-renal-cerebral-metabolic axis acts as a co-regulatory network where pathological interactions between downstream drivers are carried out by common drivers rather than individual organ injury. A major driving factor is the adaptation of the neuro-endocrine response, where excessive sympathetic tone (through cAMP/PKA signaling) and RAAS/MR

axis overactivation promote myocardial remodeling, glomerular hypertension, and vascular fibrosis (173–175). Together, these hemodynamic insults are accompanied by metabolic-inflammatory processes; the continuous activation of NLRP3 inflammasome and NF- κ B processes gives rise to systemic proinflammatory cytokines and uremic toxins that degrade endothelial integrity in the heart, kidneys and blood-brain barrier (176, 177). This vicious cycle is sustained by aberrant gut-brain signaling, characterized by dysregulated incretin secretion and microbiota-derived metabolites, which further destabilizes systemic energy homeostasis (178–180). Thus, the axis is a universal entity in which the therapy of treatment depends on those converging metabolic centers.

In general, the TyG index and other other indicators (e.g., TyG-BMI) are solid surrogate measures of insulin resistance and might be useful for therapeutic decision-making (181–183). Rather than serving merely as prognostic indicators for specific organ outcomes, elevated TyG levels should act as a “metabolic red flag” to trigger upstream interventions. Mechanistically, insulin resistance—quantified by the TyG index—amplifies systemic inflammation and oxidative stress, which are key drivers of multi-organ injury (184). As a result, in patients with high TyG indexes, therapies targeting insulin sensitivity and metabolic inflammation could be beneficial than agents targeting only glucose. This marker-guided treatment can detect “metabolic-inflammatory” phenotypes early and thus a clinician may prioritize agents interrupting the downstream drivers of the cardio-renal-cerebral-metabolic vicious cycle (185).

Examining such multidimensional regulation mechanisms can also be used as a theoretical basis for designing integrated therapies as summarized in Table 2, highlighting multi-organ injury in diabetes and offering biologically available targets for cross-organ treatment.

7 Conclusion

The therapeutic paradigm of T2D has undergone a major evolution from traditional glycemic control to multi-system integrated regulation centered on the cardio-renal-cerebral-metabolic axis. This conceptual update stems from redefining the disease: T2D is not merely a metabolic disorder driven by insulin resistance and β -cell dysfunction but a systemic disease interconnected through neural, endocrine, and immune signaling networks. Modern therapeutic strategies that synergistically modulate the heart, kidney, brain, and metabolic systems signify a transition from “glucose-centric” management to “multi-organ protection,” substantially improving overall patient prognosis.

In clinical practice, SGLT2i, GLP-1 RAs, and ns-MRAs form the backbone of organ-protective therapy, offering multiple benefits beyond glycemic control. These pharmacologic interventions, combined with dietary modifications, exercise therapy, and other non-pharmacological approaches, act through shared mechanisms such as improving insulin sensitivity and reducing chronic inflammation to establish a multi-target, multi-level management framework. Additionally, emerging cell and gene therapies, despite

TABLE 2 Protective effects of novel antidiabetic agents on the cardio–renal–cerebral–metabolic axis: key evidence and mechanistic features.

Drug class	Cardiac protection	Renal protection	Neuroprotection and cognition	Metabolic and other benefits
SGLT2 inhibitors	Effect: Significantly reduce risk of heart failure hospitalization; some agents lower cardiovascular mortality.	Effect: Slow eGFR decline, reduce proteinuria, delay end-stage kidney disease.	Effect: Potential indirect neuroprotection (Evidence limited to observational data)	Core metabolic benefits: Promote urinary glucose excretion, modest weight loss (2–3 kg), lower blood pressure, reduce serum uric acid.
	Key evidence (HR, 95% CI): - HF hospitalization: 0.65 [0.54–0.79] (DAPA-HF) - Cardiovascular death (empagliflozin): 0.62 [0.49–0.77] (EMPA-REG OUTCOME)	Key evidence: - Renal composite endpoint (Dapagliflozin): 0.56 [0.45–0.68] (DAPA-CKD) - Significant reduction in UACR	Mechanisms: Improve systemic metabolism, reduce systemic inflammation and oxidative stress, stabilize cardiorenal function to optimize cerebral perfusion.	Unique action: Promote ketone utilization, optimize myocardial energy supply.
GLP-1 receptor agonists	Effect: Reduce major adverse cardiovascular events, particularly protective against stroke.	Effect: Lower risk of new or worsening kidney disease, significantly reduce proteinuria.	Effect: Direct neuroprotective potential, reduce dementia risk.	Core metabolic benefits: Robust weight loss (5%–10%), improved lipid profile, significant reduction of liver fat content.
	Key evidence (HR, 95% CI): - MACE: 0.86–0.88 (LEADER, SUSTAIN-6) - Nonfatal stroke (semaglutide): 0.61 [0.38–0.99]	Key evidence: - New-onset macroalbuminuria: 0.70–0.80 (LEADER Renal analysis) - Significant reduction in UACR	Mechanisms: Activation of central GLP-1 receptors, enhanced synaptic plasticity, reduced neuroinflammation, decreased Aβ deposition.	Unique action: Central appetite suppression.
Non-steroidal MRA	Effect: Reduce cardiovascular composite endpoints (MI, stroke, HF hospitalization, CV death).	Effect: Significantly slow progression of chronic kidney disease, lower risk of end-stage kidney disease.	Effect: Evidence insufficient.	Core metabolic benefits: Cardiovascular and renal protection independent of glycemic and blood pressure effects.
	Key evidence (HR, 95% CI): - CV composite endpoint: 0.86 [0.78–0.95]	Key evidence: - Renal composite endpoint: 0.82 [0.73–0.93] - Sustained ~30% reduction in UACR	Mechanisms/Implications: Systemic anti-inflammatory effects may indirectly benefit neuroinflammation; improved kidney function may reduce uremic toxin-induced brain damage.	Role: “Add-on” agent targeting cardiorenal outcomes, does not directly lower glucose.

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; MACE, major adverse cardiovascular events; CKD, chronic kidney disease; T2D, type 2 diabetes.

safety challenges, provide new avenues for fundamentally reversing disease pathology.

Future clinical application of the cardio–renal–cerebral–metabolic framework requires a transition from generalized guidelines to phenotype-driven precision medicine. Specifically, therapeutic stratification should be guided by a multi-dimensional assessment of available biomarkers. Clinical trajectories defined by eGFR and UACR levels should dictate the early initiation of SGLT-2i and nonsteroidal MRAs to prevent cardiorenal progression. For patients exhibiting metabolic-inflammatory phenotypes, TyG-related indices and MASLD markers such as FIB-4 can serve as indicators to prioritize GLP-1 RAs, leveraging their potent anti-inflammatory and antifibrotic effects. Regarding cognitive preservation, baseline cognitive metrics like the MMSE combined

with neuroimaging markers are essential to identify at-risk patients who may benefit most from the neuroprotective potential of GLP-1 RAs. Pursuing these directions will facilitate the transition from broad-spectrum management to high-precision, personalized care.

Author contributions

LZ: Investigation, Writing – review & editing, Writing – original draft, Project administration, Formal analysis. CC: Data curation, Visualization, Methodology, Conceptualization, Validation, Investigation, Resources, Supervision, Writing

– review & editing, Software, Funding acquisition, Project administration, Formal analysis, Writing – original draft. FL: Writing – review & editing, Writing – original draft. BL: Supervision, Writing – review & editing, Validation, Writing – original draft.

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