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Mini-Review

Minireview: Understanding and targeting inflammatory, hemodynamic and injury markers for cardiorenal protection in type 1 diabetes

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ABSTRACT

The coexistence of cardiovascular disease (CVD) and diabetic kidney disease (DKD) is common in people with type 1 diabetes (T1D) and is strongly associated with an increased risk of morbidity and mortality. Hence, it is imperative to explore robust tools that can accurately reflect the development and progression of cardiorenal complications. Several cardiovascular and kidney biomarkers have been identified to detect at-risk individuals with T1D. The primary aim of this review is to highlight biomarkers of injury, inflammation, or renal hemodynamic changes that may influence T1D susceptibility to CVD and DKD. We will also examine the impact of approved pharmacotherapies for type 2 diabetes, including renin-angiotensin-aldosterone system (RAAS) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) on candidate biomarkers for cardiorenal complications in people with T1D and discuss how these changes may potentially mediate kidney and cardiovascular protection. Identifying predictive and prognostic biomarkers for DKD and CVD may highlight potential drug targets to attenuate cardiorenal disease progression, implement novel risk stratification measures in clinical trials, and improve the assessment, diagnosis, and treatment of at-risk individuals with T1D.

1. Introduction

Premature cardiovascular disease (CVD) and diabetic kidney disease (DKD) are the leading causes of reduced life expectancy in people with type 1 diabetes (T1D) [1,2]. Coexistent CVD and DKD are highly prevalent in these individuals, supporting the need for early identification of new screening approaches for such complications. Several cardiorenal biomarkers are currently used to detect at-risk individuals with T1D, including estimated glomerular filtration rate (eGFR), albuminuria, and lipid biomarkers. However, while widely available and relatively inexpensive, these biomarkers have limited accuracy in predicting disease progression, especially early in the natural history [3]. The pathogenesis of diabetic heart and kidney injury in T1D is multifactorial and can be ascribed to a combination of factors including hemodynamic stress, inflammation, and hypoxia (Fig. 1). Consequently, biomarkers that reflect these factors may reveal the underlying mechanistic pathways mediating CVD and DKD progression in T1D.

Existing pharmacological interventions for cardiorenal complications associated with type 2 diabetes (T2D), such as renin-angiotensin-aldosterone system (RAAS) blockers are underused in people with T1D at cardiorenal risk, and newer treatments such as sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and non-steroidal mineralocorticoid antagonists (MRAs) have not yet been studied in people with T1D and existing cardiorenal complications [4–6]. SGLT2is block proximal tubule glucose reabsorption at the level of SGLT2 in the kidney, improving glycemic

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control in people with T2D by promoting glucosuria and accompanied by natriuresis. GLP-1RAs also exert cardiorenal benefits through weight modification by stimulating glucose-dependent insulin release at the level of the pancreas [7]. Likewise, by blocking aldosterone action at the distal nephron, non-steroidal MRAs have demonstrated protection against cardiorenal damage in people with T2D and chronic kidney disease (CKD) [8]. Taken together, these data are supportive of a protective physiological effect of these agents in individuals with T1D; however, their impact on diagnostic and prognostic factors of DKD and CVD is not well understood.

Accordingly, in this review we will summarize the currently known hemodynamic, inflammatory, and injury biomarkers for cardiorenal risk in individuals with T1D and evaluate how cardiorenal protective therapies may modify these biomarkers to mitigate CVD and DKD risk.

2. Type 1 diabetes and the inflammatory pathway

The emerging pathogenic role of inflammation in the onset and progression of kidney and cardiovascular dysfunction highlights the need to outline inflammatory biomarkers as potential clinical predictors of cardiorenal disease progression. Inflammatory biomarkers may also be used to risk stratify individuals by baseline inflammatory status, further discussed below.

2.1. Inflammation and CVD

The pro-inflammatory state in T1D may predispose individuals to cardiovascular dysfunction and investigation of inflammatory biomarkers may help further elucidate this complex interplay. Table 1 summarizes currently known inflammatory biomarkers for CVD progression in people with T1D. The EURODIAB Prospective Complications Study assessed 543 participants diagnosed with T1D at <36 years of age and reported strong associations between C-reactive protein (CRP), interleukin 6 (IL-6), and soluble tumor necrosis factor (TNF) with CVD [38]. A close association was also documented between circulating markers of endothelial dysfunction and generalized inflammation, as estimated by assessing plasma CRP, IL-6, and TNF concentrations together [39]. Likewise, the SEARCH study, which studied 553 youth with T1D, reported elevations in several traditional acute-phase inflammatory biomarkers including IL-6, CRP, and fibrinogen [40]. Similar observations were shown in individuals with moderate-to-severe kidney disease who demonstrated elevated concentrations of serum fibrinogen and CRP which independently associated with prothrombotic biomarkers, as well as CVD endpoints and mortality [41]. A growing body of evidence suggests that inflammatory biomarkers may enhance our ability to predict early CVD risk in individuals with T1D and warrants further research.

2.2. Inflammation and DKD

Several known urinary and serum biomarkers highlight an underlying pro-inflammatory state which may contribute to DKD pathogenesis in individuals with T1D (Table 1). In a *post-hoc* analysis of 74 individuals with longstanding T1D and 73 age-matched healthy controls in the

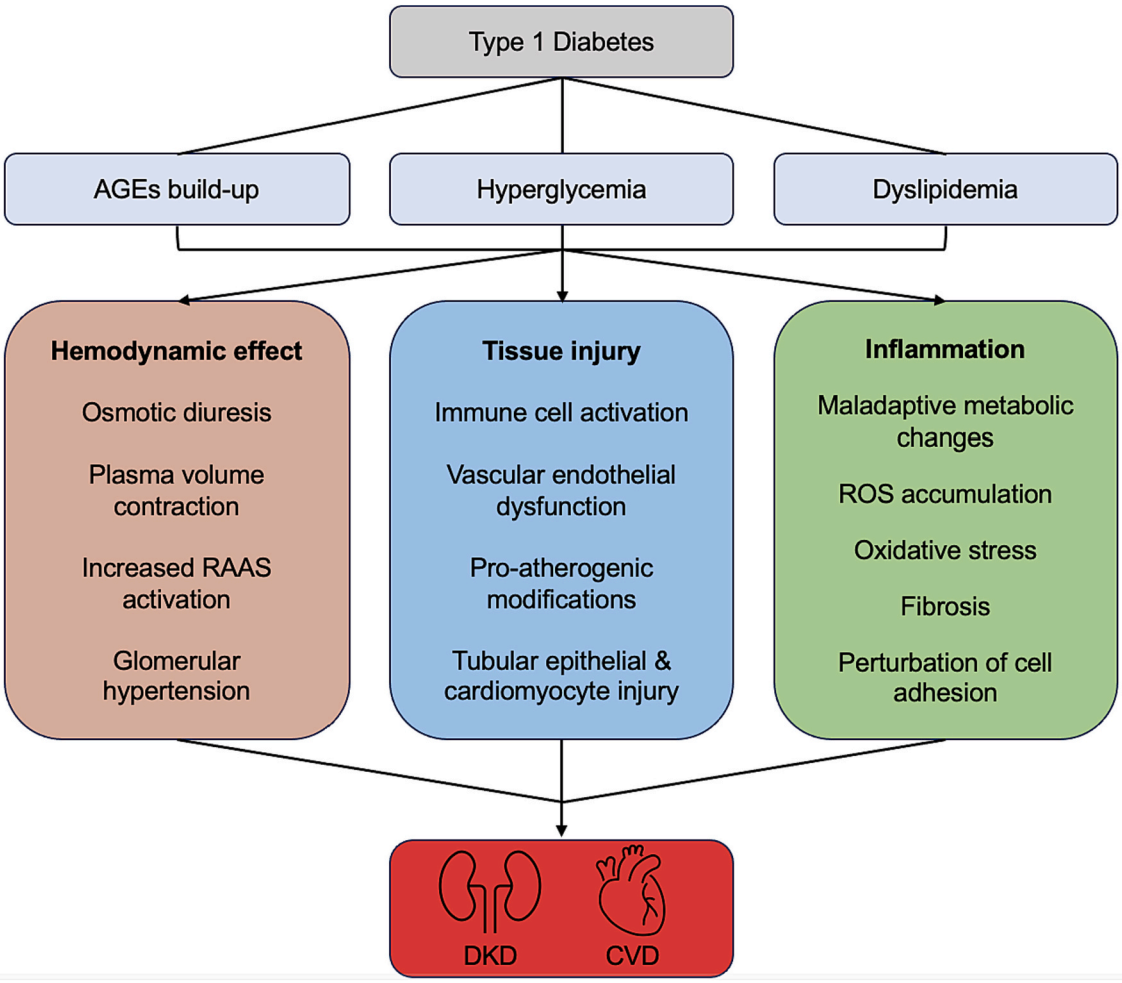

Fig. 1. Manifestation of CVD and DKD in individuals with T1D through hemodynamic perturbation, inflammation, and injury. Abbreviations: AGE, advanced glycation end-products; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species, DKD, diabetic kidney disease; CVD, cardiovascular disease.

Table 1
Summary of inflammatory and fibrotic markers for DKD and CVD outlined in individuals with T1D.

Type of marker		Diabetic kidney disease		Cardiovascular disease
		Urinary	*Circulating*	*Circulating*
Cytokines [9–18]	IL-1	–	–	↑
	IL-1β	–	↑	↑
	IL-1Rα	–	↑	↑
	IL-2	↑	↑	–
	IL-2R	–	–	↑
	IL-6	↑	↑	↑
	IL-8	↑	–	↑
	IL-10	–	–	↑ ↓
	IL-10Rβ	↑	–	–
	IL-12	↑	–	–
	IL-17F	–	↑	–
	IL-18	↑	–	–
	IP-10	↑	–	↑
	IFN-γ	–	↑	–
	IFNα2	↑	–	–
	RANTES	↑	–	–
	cys D	–	↑	–
	GM-CSF	↑	–	–
	EMAP-II	–	–	↑
TNF Family [16,17,19–21]	TNF-α	–	↑	↑
	TNF-β	–	↑	–
	TNFR	–	↑ TNFR1 ↑ TNFRSF9 ↑ TNFRSF15 ↑ TNFRSF27	↑ TNFR2
	CD27		↑ CD27	
	sCD40	↑ sCD40L ↑ CD40K	↑	↑ sCD40L
Growth factors [9,10,12]	CTGF	↑	–	↑
	FGF-2	↑	–	–
[10,15,16,18,22]	PDGF	↑ PDGF-AA ↑ PDGF-AB/BB	–	–
	PIGF	–	–	↑
	PEDF	–	–	↑
	TGF-β	–	–	↑
	VEGF	↑	↑	↑
Chemokines [10,16,17,23–26]	Eotaxin	↑	↑	–
	HMGB1		↑	↑
	MCP-1	↑	↑	↑
	MCP-3	↑	–	–
	MIP-1	↑ MIP-1α ↑ MIP-1δ [11]	↑ MIP-1β ↑ MIP-1δ	–
	MIP-3	–	↑	–
	MDC	↑	–	–
	SDF-1	–	↑	↑
	PD-L1	–	↑	–
Cell-adhesion [14,20,27]	sE-selectin	–	↑	↑ ↓
	L-selectin	–	–	↑
	sICAM-1	–	↑	↑
	sVCAM-1	–	↑	↑
	PAI-1	–	↑	↑
Fibrosis [28–30]	Fibrinogen	–	–	↑
	FPA			↑
	GAGs	↑	↑	–
	MMP	–	↑ MMP-1 ↑ MMP-2 ↑ MMP-3	↑ MMP-2
			↑ MMP-9 ↑ MMP-10	
	TIMP-1	–	↑	↑
	suPAR	↑	–	↑
	syndecan-1	–	↑	–
	UMOD	–	–	↓
Oxidative stress [31–33]	Amadori-albumin	–	↑	–
	AGE	–	↑	–
	RAGE	–	–	↓
	monocyte superoxide anion	–	–	↑
	MG-H1	–	–	↑
	MetSO	–	–	↑
	Neopterin	–	↑	–
	Nitrotyrosine	–		↑
	Pentosidine	–	↑	↑
	d-ROM	–		↑
	SOD	–		↑
	TMAO	–	↑	↑
Inflammation [34–37]	CRP		↑	↑ ↑ hs-CRP
	Glycoprotein		–	↑ GlycA ↑ GlycB ↑ GlycF
	NF-κB1	–	–	↑
	p65	–	–	↑
	pp38MAPK	–	–	↑
	SAA	–	–	↑
	tPA	–	–	↑
	UA	–	↑	–
	UTI	↑	–	–
	YKL-40	↑	–	↑

Abbreviations: DKD, diabetic kidney disease; CVD, cardiovascular disease; IL, interleukin; IP, interferon γ-induced protein; RANTES, regulated upon activation normal T cell expressed and secreted; IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1Rα, interleukin 1 receptor antagonist; CST5; cys, cystatin; IL-2R, interleukin 2 receptor; EMAP-II, endothelial monocyte-activating polypeptide-II; TNF, tumor necrosis factor; sCD40L Soluble cluster of differentiation 40 ligand; TNFR, TNF receptor type; TNFSF15, TNF superfamily member 15; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; CTGF-N, connective tissue growth factor N-terminus; PIGF, placental growth factor; TGF, transforming growth factor; PEDF, pigment epithelium-derived factor; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; SDF, stromal cell-derived factor; HMGB, high mobility group box protein; PD-L, programmed death-ligand; sVCAM-1, soluble vascular adhesion molecule-1; PAI, plasminogen activator inhibitor; sICAM, soluble intercellular adhesion molecule; sE-selectin, soluble endothelial selectin; L-selectin, leukocyte selectin; IgM, immunoglobulin M; MBL, mannose-binding lectin; Th, T helper cell; TLR, toll-like receptor; MYD88, myeloid differentiation primary response 88; PAP, plasmin/α2-antiplasmin complex; FOX3, forkhead transcription factor, suPAR, soluble urokinase plasminogen activator receptor; GAGs, glycosaminoglycans; UMOD, uromodulin; MMP, matrix metalloproteinases; TIMP-1, tissue inhibitor of metalloproteinase 1; T3C, type 3 collagen; FPA, fibrinopeptide A; AGE, advanced glycation end-products; sRAGE, soluble receptor for advanced glycation end-products; MG-H1, methylglyoxal-derived hydroimidazolone-1; SOD, superoxide dismutase, MetSO, methionine sulfoxide; d-ROM, derivatives of reactive oxygen metabolites; TMAO, trimethylamine N-oxide; YKL-40, chitinase-3-like protein 1; UTI, urinary trypsin inhibitor; UA, uric acid; CRP, C-reactive protein, hs-CRP, high-sensitivity C-reactive protein; Glyc; glycoprotein; NF-κB1, nuclear factor-κB 1, SAA, serum amyloid A; tPA, tissue plasminogen activator; pp38MAPK, p38 mitogen-activated protein kinases.

Canadian Study of Longevity in Type 1 Diabetes [42], Ambinathan et al. demonstrated a relationship between urinary inflammatory biomarkers and DKD [9]. Lower eGFR levels correlated with elevated urinary cytokines, chemokines (monocyte chemoattractant protein-1 [MCP-1] and eotaxin), and growth factors (platelet derived growth factor [PDGF] AA and vascular endothelial growth factor [VEGF] AA) [9], which is similar to previous findings in individuals with T2D and DKD [43]. Higher excretion rates of MCP-1, PDGF-AA and PDGF-BB were reported in people with T1D and hyperfiltration [10], further supporting an association between select urinary inflammatory biomarkers and abnormalities in kidney function at both ends of the spectrum.

Intriguingly, subgroup analyses in the Canadian Study of Longevity in Type 1 Diabetes identified higher concentrations of urinary IL-6 in people with T1D and DKD than DKD resistors, as defined by a preserved eGFR $\geq$60 ml/min/1.73m^2 and 24-hour urine albumin excretion within the normal range [9]. Several studies have also reported elevated concentrations of circulating IL-6 in people with T1D and contributions to incident moderate albuminuria and DKD have been hypothesized [11,44]. Potential strategies for the use of this pro-inflammatory biomarker in the risk assessment and/or treatment of people with T1D and DKD require further study. The ZEUS trial (NCT05021835) is currently investigating ziltivekimab, a human monoclonal antibody targeting IL-6, in people with CVD, CKD and systemic inflammation. Findings from the ZEUS study could be of interest for future application to individuals with high-risk T1D.

Another factor linked with kidney injury in DKD is TNFα. This cytokine plays a known role in the pathogenesis of progressive kidney disease including inflammatory changes, fibrogenesis, and kidney hypertrophy [45]. Plasma concentrations of TNFα receptor (TNFR) 1 are widely used as a surrogate marker for the TNFα system [45]. Plasma concentrations of TNFR1 and TNFR2 were strongly associated with eGFR decline in a non-albuminuric T1D cohort with normal eGFR >60 ml/min/1.73m^2 [46], as well as the Finnish Diabetic Nephropathy Study T1D cohort with elevated urinary albumin excretion (i.e., $\geq$200 μg/min or $\geq$ 300 mg/day in at least two out of three consecutive overnight or 24-h urine samples) [45]. It is notable that associations between TNFα and risk of kidney failure have only been observed with these few receptor types, and total TNFα has only modestly associated with CKD. In summary, existing literature provides ample supporting evidence for the involvement of inflammatory activity in the progression of renal failure in T1D.

3. Hemodynamic and injury markers in DKD

Hyperglycemia in T1D results in a combination of maladaptive responses that promote hemodynamic stress, including increased plasma renin activity with subsequent activation of the RAAS, vasoconstriction, salt and water retention, renal vascular resistance, increased myocardial contractility, and sympathetic nervous system activation [47]. Over 80 % of individuals with T1D may have intrarenal RAAS activation which, in turn, raises single nephron intraglomerular pressure and is a key determinant in the development of DKD [48]. Identifying key biomarkers that highlight the progression of intraglomerular and systemic hemodynamic dysfunction may allow for targeted therapeutics to treat or prevent hemodynamic stress in T1D, including the use of RAAS inhibitors, and possibly other emerging therapeutics (Table 2).

3.1. Intraglomerular hemodynamics in T1D with hyperfiltration

Glomerular hyperfiltration is a physiologic adaptation to a reduction in functional nephron mass secondary to injury, resulting in increased intraglomerular pressure and filtration. This process is hypothesized as an early step in the pathway to irreversible nephron damage and DKD [56]. Škrtić et al. demonstrated in 73 adults with T1D that hyperfiltration (GFR $\geq$135 ml/min/1.73m^2) was associated with greater renal plasma flow (RPF) and intraglomerular pressure, as well as lower pre-glomerular and similar post-glomerular arteriolar resistance when compared to normal filtration (GFR 90–134 ml/min/1.73m^2) in T1D [57]. The authors proposed that hyperfiltration was largely associated with reductions in pre-glomerular resistance than increases in post-glomerular resistance. This association was also supported by a cross-sectional study which demonstrated elevated RPF and lower pre-glomerular pressure in young adults with T1D compared to controls [58]. Additionally, in a youth T1D cohort with or without hyperfiltration (GFR $\geq$135 ml/min/1.73m^2), Sochett et al. reported that exposure to a graded angiotensin-II infusion under euglycemic conditions resulted in a significant decline in RPF and GFR in the hyperfiltration group but not in the normofiltration group. Treatment with RAAS blockade followed by repeat testing resulted in a decrease in GFR without full normalization in the hyperfiltration group, suggesting a role for post-glomerular arteriole dilation and RAAS activation in progressive DKD [59]. The rise in intraglomerular pressure as a result of chronic RAAS activation is related to fluid shear stress and wall tension, leading to local and systemic fibrosis and pro-inflammatory effects [59]. Therefore, pre-glomerular arteriolar dilation, as well as post-glomerular vasoconstriction, may serve as an early marker of RAAS-mediated renal dysfunction and progressive DKD as well as a therapeutic target for early stage DKD in the setting of T1D.

Table 2
Summary of hemodynamic parameters for DKD and CVD outlined in individuals with T1D [49–55].

Type of marker		Diabetic kidney disease	Cardiovascular disease
Metabolic	Copeptin	↑	↑
	Preptin	–	↑
	Transferrin	↑	–
	NO	–	↓
Central hemodynamics	AIMT	–	↑
	CIMT	–	↑
	CADP	↓	↓
	CASP	↑	↑
	CPP	↑	↑
	RI	↑	–
	SEVR	↓	↓
Local hemodynamics	ACE	↑	↑
	AGT	↑	–
	AGP-2	–	↑
	ANP	–	↑
	MR-proANP	↑	↑
	NT-proBNP	–	↑
	catecholamine	–	↑
Thrombosis	D-dimer	↑	↑
	F(1 + 2)	–	↑
	Heparan sulfate	–	↓
	PAI-1	–	↑
	PMP	–	↑
	TAT	–	↑
	vWFCP	↑	–

Abbreviations: DKD, diabetic kidney disease; CVD, cardiovascular disease; NO, nitric oxide; RI, CASP, central aortic systolic pressure; CPP, central aortic pulse pressure; CADP, central aortic diastolic pressure; SEVR, subendocardial viability ratio; CIMT, carotid intima-media thickness; AIMT, aortic intima-media thickness; ACE, angiotensin-converting enzyme, AGT, angiotensinogen; ANP, atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; AGP-2, angiopoietin-2; vWFCP, von Willebrand factor-cleaving protease; F(1 + 2), prothrombin fragment 1 + 2; TAT, thrombin–antithrombin III complex; PAI-1, plasminogen activator inhibitor-1; PMP, platelet microparticles.

3.2. Kidney injury markers in DKD

Despite the high risk of long-term kidney failure as a consequence of DKD in people with T1D, early DKD tends to progress silently without overt clinical symptoms for years [60,61]. Accordingly, early recognition of kidney injury through biomarker-based screening tools may help

mitigate progression of severe disease and serve as a valuable tool for DKD risk reduction in individuals with T1D (Table 3).

Kidney injury molecule-1 (KIM-1), a well-recognized acute tubular injury marker, and β_2 microglobulin (B2M), a dual tubular and glomerular injury marker, are robustly associated with kidney outcomes, including progressive CKD [67], DKD [62,68] and acute kidney injury [69]; yet, the role of each of these renal injury markers in T1D is still being fully explored. KIM-1 and B2M are strong predictors of eGFR decline and kidney failure, regardless of DKD status, in adults with T1D [63,70,71], but KIM-1 fails to predict kidney decline independent of changes in urinary albumin excretion [72], warranting further investigation into the association between KIM-1, albuminuria, and hard renal outcomes. Uromodulin, a protein exclusively expressed in the thick ascending limb of the loop of Henle, may also serve as a valuable marker of renal tubular function at the thick ascending limb. Higher plasma concentrations of uromodulin correlate with a lower risk of albuminuria and impaired eGFR in people with T1D [63], suggesting a renoprotective role at elevated concentrations. In people with longstanding T1D and DKD, uromodulin concentrations are lower than healthy controls, but this reduction did not correlate with intrarenal hemodynamic dysfunction [62]. Taken together, in early DKD, elevated serum uromodulin levels may confer protection against the development of DKD by way of a combination of effects including immunomodulation and regulation of ion transport across the thick ascending limb [73]. Further research is required to complete our understanding of uromodulin in T1D and whether it can be used as a prognostic tool for the detection of DKD.

Early DKD can also be characterized by progressive glomerular disease ascribed to podocyte injury. Recently, significant associations between urinary podocyte-derived microparticles and eGFR were observed exclusively in a cohort of young persons with T1D [74]. The formation and release of podocyte-derived microparticles in urine is associated with pro-fibrotic responses at the level of the proximal tubule and is involved in pathogenic mechanisms leading to tubulointerstitial fibrosis and DKD [75]. Urinary profiles of podocalyxin, synaptopodin, alpha-actinin-4, and podocin are correlated with severe albuminuria, kidney injury and DKD progression [76], as well as inflammatory VEGF-A and MCP-1 in podocyturia [9]. Sources of reactive oxygen species, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and co-player transient receptor potential canonical (TRPC) 6 are likely major drivers of podocyte injury which are related to diabetic nephropathy [77]. As such, podocyte injury is an early determinant of kidney function decline and may play an important role in early DKD.

Table 3
Summary of injury markers for DKD and CVD progression in people with T1D [21,62–66].

	DKD	CVD
Urinary	↑ NAG	↑ NAG
	↑ B2M	↑ NCR
	↓ CathL	
	↑ CathD	
	↑ HSP70/Cr	
	↑ IL-9	
	↑ KIM-1	
	↑ L-FABP	
	↑ NGAL	
	↑ orosomucoid	
	↑ OPN	
	↓ pi-GST	
	↑ RBP	
	↑ T4C	
	↓ UMOD	
	↑ VDBP	
Circulating	↑ vWF	↑ vWF
	↑ A1M	↑ CT-1
	↑ B2M	
	↑ CD27	
	↑ cys C	
	↑ KIM-1	
	↑ NGAL	
	↓ NGAL	
	↑ orosomucoid	
	↑ T3C	

Abbreviations: DKD, diabetic kidney disease; CVD, cardiovascular disease; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; T4C, type 4 collagen; RBP, retinol binding protein; IL, interleukin; Cath, cathepsin; NAG, *N*-acetyl-β-d-glucosaminidase; VDBP, vitamin D-binding protein; L-FABP, liver-type fatty acid binding protein; HSP, heat shock protein; Cr, creatinine; B2M, β_2 microglobulin; OPN, osteopontin; pi-GST, glutathione S-transferase pi; NCR, NAG-to-creatinine ratio, vWF, von Willebrand factor; CD27, cluster of differentiation 27; A1M, α_1-microglobulin; cys C, cystatin C.

4. Hemodynamic and injury markers for cardiovascular dysfunction in T1D

Hemodynamic mediators are widely used in clinical practice to predict cardiovascular risk, identify early cardiac dysfunction, and evaluate for heart failure (HF) progression in people with diabetes who are at high risk. Yet, despite our growing understanding of diabetes-associated CVD, the extent of knowledge specific to individuals with T1D is quite limited.

Biomarkers associated with HF progression can be used to improve diagnosis and prognosis of diabetes-related cardiovascular complications (Table 2). Currently, natriuretic peptides, particularly *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), are widely used diagnostic indicators for HF [78], irrespective of diabetes status [79]. Natriuretic peptides are released in response to elevated intracardiac pressures and fluid overload [78]. Likewise, midregional proatrial natriuretic peptide (MR-proANP) has reported associations with previous cardiac events in individuals with T1D, as well as renal dysfunction and albuminuria [49]. Recently, galectin-3 (Gal-3), a carbohydrate-binding protein, was also described as a novel prognostic biomarker for HF [80], although some studies have reported a weaker association with HF progression than NT-proBNP [81]. Gal-3 is involved in the regulation of multiple cell processes, including nephrogenesis, cardiorenal inflammation and fibrosis [82], as well as the development of pulmonary hypertension by way of vascular remodeling and oxidative stress [83], but associations with HF in T1D have yet to be investigated.

It is widely recognized that people with HF are at substantial risk for thrombotic complications. In individuals with T1D, elevated concentrations of prothrombin fragment 1 + 2 and thrombin–antithrombin III complex are observed, most notably in people at risk of venous thromboembolism and diabetic microangiopathy [50]. The rise in plasminogen activator inhibitor 1 (PAI-1) in people with T1D at risk of HF and CVD further supports this process, as inhibition of plasminogen can lead to a physiologic reduction in clot breakdown [84]. The resulting increase in blood clots further upregulates D-dimer, a by-product of the clotting process, and can serve as a HF biomarker in people with T1D [50]. Yet, despite our growing understanding of diabetes-associated HF progression, further research is needed to expand our armamentarium of screening tools for HF in people with T1D.

5. Pharmaceutical interventions in type 1 diabetes

5.1. Impact of RAAS blockade on inflammation

RAAS blockers have traditionally served as the standard of care for cardiorenal protection for people with diabetes and early DKD and/or CVD. However, in people with T1D, prevention or attenuation of kidney disease onset and progression solely through RAAS inhibition may be clinically insufficient [85]. Other mechanisms including the presence of low-grade inflammation, oxidative stress, and hemodynamic change may work in conjunction with RAAS to exacerbate the disease state. Furthermore, blockade of RAAS may help attenuate DKD and CVD progression through the mitigation of chronic inflammation [86], but this may not fully assuage the underlying pathology.

Up to 40 % of individuals receiving RAAS blockade still exhibit high aldosterone concentrations, a phenomenon referred to as "aldosterone breakthrough" [87]. Treatment with 60 days of spironolactone, a steroidal MRA, in addition to standard RAAS blocker therapy, resulted in no changes to markers of inflammation, including TNFα, IL-6, IL-8, IL1β, and CRP in a cohort of individuals with T1D [88]. Despite a known multifactorial role in both blood pressure and RAAS mediation, additive spironolactone treatment therefore did not confer additional anti-inflammatory effects in individuals with T1D. Consequently, the impact of RAAS blockade on inflammation requires further exploration, particularly in combination with other agents. Finerenone, a selective non-steroidal MRA with demonstrable cardiorenal protective effects in people with T2D and CKD [8], may offer alternative treatment options for T1D to address the risk of hyperkalemia and diabetic ketoacidosis (DKA) while maintaining cardiorenal benefits. Its use in people with T1D and CKD is currently being studied in the FINE-ONE (NCT05901831) trial.

5.2. SGLT2 inhibition, GLP-1RAs, hemodynamics and inflammation

Although several studies have described the cardiorenal benefits exhibited with SGLT2i usage, it is important to note that SGLT2is have not yet been approved as treatment for T1D in most countries, and the effect of SGLT2is on the inflammatory, fibrotic, and hemodynamic changes in T1D remain unknown (Table 4).

Partly due to a natriuresis-related effect, SGLT2is are associated with several systemic and renal hemodynamic changes that are physiologically linked with attenuation of cardiovascular and kidney risk [89–91]. The initial transient plasma volume contraction that is accompanied by natriuresis triggers a compensatory activation of the RAAS, and thereby attenuates expression of NT-proBNP and ANP and increases circulating levels of renin, angiotensin-II, and aldosterone [4,89,90,92]. As a result of intrarenal hemodynamic alterations, SGLT2is also cause a transient dip in GFR and lower albuminuria and attenuate glomerular hyperfiltration [4]. This reduction in intraglomerular hypertension, RAAS overactivation and sympathetic nervous activity with SGLT2is may also help attenuate renal fibrosis. This may, in part, be attributed to mitigation of the hyperglycemia-induced pathological shift in energy metabolism from glycolysis to fatty acid oxidation. By alleviating renal hypoxia through this metabolic switch, SGLT2 inhibition reduces hypoxia-inducible factors (HIF)-1 activity and promotes HIF-2α signaling, thus improving oxygen delivery, fibrosis, and inflammation in the diabetic kidney [93]. SGLT2is also cause an increase in hematocrit [91], which may be associated with improved myocardial and kidney oxygen delivery [94]. Experimental models of T1D have reported reductions in markers of renal tissue inflammation, tubular injury and fibrosis with SGLT2is, suggesting a potential protective role against DKD progression in people with T1D (Table 5) [95,96].

Yet, one important consideration with SGLT2i treatment in people with T1D is the generation of systemic ketones, an ancillary glucose-independent source of energy with anti-inflammatory and anti-oxidative effects [98]. While ketone bodies may exhibit some degree of cardiorenal protective effects, a rise in ketones without matched insulin exposure can lead to DKA, a potentially life-threatening complication in people with T1D. To attenuate DKA risk while on treatment with an SGLT2i in individuals with T1D, frequent and/or continuous ketone monitoring has been used in clinical trials.

Similar to SGLT2is, there is strong rationale supporting off-label use of GLP-1RAs in T1D due to anti-inflammatory, antioxidant, and insulin-sensitizing effects, as well as clinical evidence demonstrating cardiorenal protection in other populations. These potential beneficial physiologic effects include reductions in BNP, CRP, TNFα, and adiponectin [99]. GLP-1 RA therapies also stimulate natriuresis through RAAS and non-RAAS dependent pathways and attenuate reactive oxygen species in experimental studies, thereby delaying DKD progression [100]. Importantly and in contrast to SGLT2is, repurposing of GLP-1RAs

Table 4
Summary of major cardiorenal protective findings in phase III clinical trials for SGLT2i treatment in participants with T1D. Results are placebo-subtracted mean differences in SBP, eGFR, and UACR, from baseline.

Study	Inclusion criteria	Treatment	Dose (mg)	Major findings (95 % confidence interval)
EASE-2 and -3 [89]	T1D HbA1c: 7.5–10.0 % C-peptide <0.7 ng/mL eGFR ≥30 mL/min/1.73 m^2 Age ≥ 18 years ≥ 12 months on insulin[1,2]	26[3] or 52[4] weeks of empagliflozin or placebo (n = 1:1:1, 730)[4] (n = 1:1:1:1, 975)[3]	2.5	SBP: −2.1 mmHg (−3.9, −0.2); $p < 0.05$ eGFR: −0.1 ml/min/1.73m^2; NS[3] UACR: NS
			10	SBP: −3.9 mmHg (−5.7, −2.1); $p < 0.0001$ eGFR: −2.0 ml/min/1.73m^2 (−4.0, −0.1); $p < 0.05$[4] UACR: −16 %; NS[5] Hypoglycemia [N(%)]: 20 (4.1 %); Placebo: 15 (3.1 %) DKA [N(%)]: 21 (4.3 %); Placebo: 6 (1.2 %)
			25	SBP: −3.7 mmHg (−5.6, −1.9), $p < 0.0001$ eGFR: −2.0 ml/min/1.73m^2 (−4.0 to −0.4); $p < 0.05$[4] UACR: −30 %; $p < 0.05$[5] Hypoglycemia [N(%)]: 13 (2.7 %); Placebo: 15 (3.1 %) DKA [N(%)]:16 (3.3 %); Placebo: 6 (1.2 %)
DEPICT-1 and − 2 [90]	T1D HbA1c: 7.7–11.0 % UACR ≥ 30 mg/g C-peptide <0.7 ng/mL Age: 18–75 years BMI ≥ 18.5 kg/m^2 ≥ 12 months on insulin[1,6,7]	52 weeks of dapagliflozin (two doses) or placebo (n = 1:1:1, 747)[8] (n = 1:1:1, 717)[9]	5	SBP: −5.37 mmHg (−9.26, −1.49) eGFR: −3.27 ml/min/1.73m^2 (−0.92, 7.45); NS UACR: −13.3 % (−37.2, 19.8) Hypoglycemia [N(%)]: 8 (1.5 %); Placebo: 5 (0.9 %) DKA [N(%)]: 22 (4.0 %); Placebo: 6 (1.1 %)
			10	SBP: −4.73 mmHg (−8.58, −0.88) eGFR: −2.12 ml/min/1.73m^2 (−2.03, 6.27); NS UACR: −31.1 % (−49.9 to −5.2)

(continued on next page)

Table 4 (*continued*)

Study	Inclusion criteria	Treatment	Dose (mg)	Major findings (95 % confidence interval)
				Hypoglycemia [N(%)]: 5 (0.9 %); Placebo: 5 (0.9 %) DKA [N(%)]: 20 (3.5 %); Placebo: 6 (1.1 %)
inTandem 1–3 [91]	T1D Diagnosed for ≥ 1 year HbA1c: 7.0–11.0 % β-hydroxybutyrate levels ≤0.6 mmol/L[10] eGFR ≥45 mL/min/1.73m^2 [11] Age ≥ 18 years Insulin-treated	52 weeks of sotagliflozin (two doses) or placebo (n = 1:1:1, 787)[10] (n = 1:1, 1402)[11]	200	SBP: −2.8 mmHg (−5.7, −0.9); $p < 0.01$[10] −1.3 mmHg (−2.5, −0.1); $p < 0.05$[12] eGFR: −1.96 ml/min/1.73m^2 (−3.45, −0.47); $p = 0.01$[13] UACR: −23.7 % (−48.9, 1.5); NS[5,13] Hypoglycemia [N(%)]:17 (6.5 %); Placebo: 26 (9.7 %) DKA [N(%)]: 9 (3.4 %); Placebo: 1 (0.4 %)
			400	SBP: −4.4 mmHg (−6.4, −2.5); $p < 0.001$[10] −0.6 mmHg (−1.8, 0.6); NS[12] eGFR: −0.49 ml/min/1.73m^2 (−1.99, 1.00); NS[13] UACR: −18.3 % (−45.3, 8.7); NS[5,13] Hypoglycemia [N(%)]: 38 (4.0 %); Placebo: 43 (4.5 %) DKA [N(%)]: 32 (3.3 %); Placebo: 4 (0.5 %)

Abbreviations: T1D, type 1 diabetes; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio; DKA, diabetic ketoacidosis; BMI, body mass index; MDI, multiple daily injections; CSII, continuous subcutaneous insulin infusion.

[1] If MDI, injections should be administered ≥3 times per day.

[2] If CSII, ≥5 months of experience is required.

[3] After 26 weeks of treatment in EASE-3.

[4] After 52 weeks of treatment in EASE-2.

[5] Observed in participants with baseline UACR ≥30 mg/g.

[6] Insulin administration method (MDI or CSII) is unchanged for ≥3 months prior to screening.

[7] Dosage of insulin ≥0.3 U/kg/day for ≥3 months prior to screening.

[8] Analysis performed in DEPICT-1 cohort.

[9] Analysis performed in DEPICT-2 cohort.

[10] Analysis performed in inTandem 1 cohort.

[11] Analysis performed in inTandem 3 cohort.

[12] Analysis performed in inTandem 2 cohort.

[13] Pooled analysis of inTandem 1 and 2 cohorts.

Table 5
Summary of the effect of SGLT2i on inflammatory, fibrotic, and oxidative stress biomarkers, as well as hemodynamic and injury markers in experimental models of T1D [95–97].

Type of marker		Effect
Chemokines and cytokines	MCP-1	↓
	IL-1B	↓
	IL-6	↓
Cell-adhesion	ICAM-1	↓
Inflammation	AP-1	↓
	p21	↓
	p27	↓
	CD14	↓
	NF-κB	↓
	TNF	↓
	TLR2	↓
	TLR4	
Thrombosis	PAI-1	↓
Growth factor	TGF-β	↓
	CTGF	↓
Fibrosis	T4C	↓
	TIMP-2	↓
	Fibronectin	↓
Hemodynamics	ANP	↓
	BNP	↓
Oxidative stress	Renal RAGE	↓
	HO-1	↓
	8-OHdG (urinary)	↓
	L-FABP (urinary)	↓
	LOX-1	↓
Injury	KIM-1 (urinary)	↓
	NGAL (urinary)	↓
	cTnI	↓

Abbreviations: MCP, monocyte chemoattractant protein; ICAM, intercellular adhesion molecule; PAI-1, plasminogen activator inhibitor-1; TGF, transforming growth factor; CTGF, connective tissue growth factor; RAGE, receptor for advanced glycation end-products; 8-OHdG, 8-hydroxydeoxyguanosine; L-FABP, liver-type fatty acid binding protein; p21, cyclin-dependent kinase inhibitor 1; p27, cyclin-dependent kinase inhibitor 1B; HO-1, heme oxygenase-1; CD, cluster of differentiation; NF-κB, nuclear factor-κB; IL, interleukin; TIMP-2, tissue inhibitor of metalloproteinase-2; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; TNF, tumor necrosis factor; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; TLR, toll-like receptor; AP-1, activator protein 1; T4C, type 4 collagen; LOX-1, lectin-like oxidized low-density lipoprotein receptor 1; ACAT, acyl-coenzyme A:cholesterol acyltransferase 1, ABCA1, ATP-binding cassette transporter A1.

for people with T1D is additionally appealing as the risk of DKA does not appear to be increased with these agents, though it is somewhat balanced by a higher risk of hypoglycemia. Nevertheless, further work is required in people with T1D to better understand the risk-benefit ratio of these therapies in people at the highest risk of complications.

6. Conclusion

CVD and DKD in individuals with T1D are mediated by a combination of factors including hemodynamic stress, renal and cardiac injury, and inflammation. Identifying unique biomarkers for these processes may help with the early identification and optimized treatment of individuals at risk of heart and kidney disease. Cardiorenal protective therapies like SGLT2is, non-steroidal MRAs, and GLP-1RAs may serve as potential therapeutic options for people with T1D to target pathophysiologic processes independent of hyperglycemia. Considering the known cardiorenal benefits of these therapies in populations with T2D, studying these agents in T1D is of major interest; however, the potential for precipitating euglycemic DKA with SGLT2i usage should be strongly considered, as well as strategies for DKA mitigation in clinical trials and future practice. Advancements in our mechanistic understanding of cardiorenal disease development are essential for the development of novel future treatments that move beyond the correction of insulin deficiency and hyperglycemia-induced injury in people with T1D.

Abbreviation list

B2M	β_2 microglobulin
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
eGFR	Estimated glomerular filtration rate
Gal-3	Galectin-3
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
HIF	Hypoxic inducible factor
IL	Interleukin
KIM-1	Kidney injury molecule 1
MCP-1	Monocyte chemoattractant protein-1
MR-proANP	Midregional proatrial natriuretic peptide
MRA	Mineralocorticoid receptor agonist
NADPH	Nicotinamide adenine dinucleotide phosphate
NT-proBNP	*N*-terminal pro-B-type natriuretic peptide
PAI-1	Plasminogen activator inhibitor 1
PDGF	Platelet derived growth factor
RAAS	Renin-angiotensin-aldosterone system
RPF	Renal plasma flow
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TRPC	Transient receptor potential canonical
VEGF	Vascular endothelial growth factor

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