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Diabetic Kidney Disease in Adolescents with Type 2 Diabetes: New Insights and Potential Therapies

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Abstract

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) and dialysis in the Western world. Early DKD, including microalbuminuria and renal hyperfiltration, are common in adolescents with type 2 diabetes (T2D). Furthermore, youth-onset T2D carries a higher risk of progressive DKD than adult-onset T2D of similar diabetes duration. DKD is characterized by a long clinically-silent period without signs of disease. Therefore, a major challenge in preventing DKD is the difficulty in identifying high-risk T2D patients at an early stage.

The Type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated a high initial prevalence that increased over time, irrespective of treatment arm. This key observation underscores the importance of discovering new therapeutic targets to supplement conventional management, in order to reduce DKD risk.

In this review, we focus on early DKD in T2D and summarize potential novel biomarkers and therapeutic targets.

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Compliance with Ethics Guidelines

Conflict of Interest

Petter Bjornstad and Kristen J. Nadeau declare that they have no conflict of interest. David Z. Cherney has received speaker honoraria from Janssen, AstraZeneca, Boehringer-Ingelheim, Lill,y and Merck and has received research grant support from AstraZeneca, Merck, Astellas, and Boehringer-Ingelheim. David M. Maahs is on the advisory board for Insulet and his institution has received research support from Dexcom and Medtronic.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Glomerular filtration rate (GFR); cystatin C; creatinine; iohexol; diabetic kidney disease; renal hyperfiltration; rapid GFR decline; albuminuria; impaired GFR

Introduction

Diabetic kidney disease (DKD) remains a leading cause of morbidity and mortality in people with type 2 diabetes (T2D) (1–3). The 2011 US Renal Data System reported that DKD accounted for 44.5% of all cases of end-stage renal disease (ESRD) (4). In 2009, overall Medicare expenditure for people with chronic kidney disease (CKD) and diabetes accounted for $18 billion (4). The prevalence of DKD has remained fairly stable over the last 20 years, despite increasing prevalence of T2D (5, 6), likely related to improved glycemic, blood pressure and weight control, since evidence-based therapies directly targeting DKD are scarce. Markers of early DKD, including microalbuminuria and renal hyperfiltration, are common in youth with T2D (7). For example, we previously reported a prevalence of 34% for microalbuminuria and 24% for renal hyperfiltration in adolescents with T2D with a mean age of 15 years (7). Moreover, the Type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated that microalbuminuria is common in youth with an average T2D duration of only 6 months and reported a 2.5 fold increase in the occurrence of microalbuminuria over an average follow-up of 3.9 years (8). Since signs of DKDare already present at diabetes diagnosis in youth with T2D, early interventions may be the most likely to prevent progression of DKD.

Youth-onset T2D carries a particularly high risk of progressive DKD, which is significantly greater than youth with type 1 diabetes (T1D) or adults with T2D of similar disease duration (8–15). In fact, adolescents with T2D have a two-fold increased risk of microalbuminuria compared to youth with T1D (8, 10, 16). Risk factors for DKD in T2D include female sex, obesity, triglycerides, hyperglycemia, hypertension, cardiovascular disease, insulin resistance, and elevated uric acid (17–21) [Figure 1].

There are limited longitudinal data available on the natural history of DKD in youth with T2D (22). Microalbuminuria may precede the onset of T2D in insulin-resistant obese adolescents (23, 24). In addition, hyperfiltration is thought to be a major contributing factor for DKD in T2D, reflecting underlying increased intraglomerular pressure leading to structural changes over time, such as mesangial expansion and glomerular basement membrane thickening (25). Obesity and impaired glucose tolerance are associated with hyperfiltration (25–29), suggesting that renal injury occurs very early in the disease process (30), possibly prior to development of T2D. It is also noteworthy that a significant proportion of patients do not follow this classical trajectory of microalbuminuria and normal-to-elevated glomerular filtration rate (GFR), followed by proteinuria and GFR decline; instead, these patients exhibit an accelerated GFR decline in the absence of proteinuria (17–21). The loss of renal function in the absence of albuminuria highlights the need to identify alternate biomarkers that better capture early DKD risk.

By the time GFR is below 60mL/min/1.73m^2, approximately half of renal function is lost, with well-established renal structural changes that are usually refractory to therapeutic strategies, including improved blood pressure and glycemic control (31, 32). While there are reports demonstrating associations between glycemic control, insulin sensitivity, and DKD in youth with T2D (7, 8), additional longitudinal data are required to further characterize these relationships and to identify novel and modifiable risk factors that contribute to the development and progression of early DKD. Understanding these risk factors may enable us to identify individuals at high risk of early DKD and to intervene prior to permanent kidney injury. In this review, we focus on early DKD in T2D and summarize risk factors, early biomarkers and therapeutic targets for this condition.

Risk factors for DKD in youth with T2D

i. Microalbuminuria

Microalbuminuria, defined as albumin-to-creatinine ratio ≥30mg/g or an albumin-excretion-rate ≥200ug/min, has been used as a marker of renal and systemic vascular dysfunction (33) and metabolic risk in adults and adolescents with prediabetes and T2D (34), (35). The implications of having microalbuminuria are, however, controversial, since microalbuminuria regresses to normoalbuminuria in a significant proportion of adults with T2D (36). Proposed determinants of albuminuria regression include blood pressure and glycemic control (36) but are not well defined in adolescents with T2D. In adults with T1D, estimated insulin sensitivity at baseline was predictive of microalbuminuria regression over 6-years of follow up [odds ratio: 2.5, 95% confidence interval 1.3–4.9, p= 0.006] (37). Similarly, in our cross-sectional analysis of adolescents with T2D, one standard deviation increase in measured insulin sensitivity by the hyperinsulinemic-euglycemic clamp technique was associated with lower odds of having microalbuminuria [odds ratio: 0.41, 95% confidence interval 0.17-0.99, p=0.047] (7). For these reasons, insulin sensitivity may hold promise as a modifiable risk factor for microalbuminuria in adolescents with pre-diabetes and T2D.

ii. Renal hyperfiltration

Early DKD phenotypes, such as renal hyperfiltration and rapid GFR decline, are considered strong risk factors for progression to CKD and ESRD and may predict progressive DKD prior to loss of renal function (38–42). For that reason, GFR may be a more clinically relevant measure of early nephropathy than albuminuria in diabetes. As a result, the American Diabetes Association, National Kidney Foundation and International Society of Nephrology recommend annual measurement of estimated GFR to identify and monitor DKD (43–45).

Renal hyperfiltration is typically defined as a GFR of between 120 mL/min and 150 mL/min/1.73m^2, or greater than 2 standard deviations above the mean GFR in normal, healthy individuals (46), and is thought to represent the earliest hemodynamic abnormality seen in diabetes (27, 38, 47). Individuals with T2D frequently exhibit a significant increase in GFR, with the prevalence of renal hyperfiltration reported to range between 5-40% (27, 38), predisposing this population to progressive renal disease (27). The pathogenesis of

hyperfiltration in T2D is incompletely understood but has been attributed to glomerular hemodynamic and tubular factors (48). Hyperfiltration has also been documented to occur in individuals with glucose intolerance before the diagnosis of T2D (49, 50). Additionally, obesity and impaired glucose tolerance are associated with renal injury that is pathophysiologically and histologically similar to classical diabetic nephropathy (27–29, 51), suggesting that the renal insult may begin prior to the development of frank hyperglycemia (30). For example, a recent report demonstrated increased estimated GFR in adolescents with pre-diabetes and overweight adolescents compared to lean controls (35).

iii. Rapid GFR decline

Rapid GFR decline, commonly defined as annual loss greater than 3mL/min/1.73m^2 or >3.3%/year, is considered a stronger predictor of progressive DKD than albuminuria in T1D (52–57), but data in T2D are less consistent (58). In Pima Indians with T2D, rapid GFR decline is frequently present prior to the onset of macroalbuminuria and the GFR slope over time is reported to be almost as predictive of ESRD as albuminuria (58). In contrast to data from adults with T1D, progression to ESRD was strongly dependent on progression to macroalbuminuria (58). Given the importance of rapid GFR decline and current lack of data, longitudinal assessments of GFR trajectories in adolescents with T2D are needed.

iv. Estimation and measurement of GFR in T2D

Although there are several equations available to estimate GFR in children and adolescents using endogenous filtration markers (serum creatinine and/or cystatin C), to our knowledge no single equation has been specifically developed or validated in adolescents with T2D. The Schwartz creatinine-based equation from 2009 is the most widely used in clinical practice, but with its most accurate range being between 25-75 mL/min/1.73m^2 (59), this equation is less useful in adolescents with T2D who usually have GFR values above this range (27, 38, 40, 41). Stronger agreement with measured GFR was demonstrated with cystatin C (e.g. Zappitelli and Berg) (60–62) and combined creatinine and cystatin C equations (e.g. CKiD, Zappitelli, Schwartz, Bouvet combined creatinine and cystatin C equations) (59–61, 63, 64) compared to creatinine equations (59–64). While both serum creatinine and cystatin C are affected by factors other than GFR, cystatin C is considered to be less biased by age and weight compared to creatinine-based measurements and correlates more closely with direct measures of GFR over a wide spectrum of plasma glucose levels (65, 66). Despite the possible superiority of cystatin C compared to creatinine, currently available estimates of GFR remain imperfect (67–69) and there are no currently published equations validated against measured GFR in youth with T2D.

A recent DCCT-EDIC paper reported that changes in eGFR over a 3 year period may not reflect changes in measured GFR (70, 71). This is of particular concern in adolescents and young adults with diabetes, in whom renal hyperfiltration is present in approximately 50% of individuals (38, 46). The dissociation between changes in eGFR and measured GFR is of further concern since rapid changes in GFR may be missed due to a lack of acceptable screening methods for subtle changes in renal function (56). Perrin et al. reported that most GFR estimations fail to detect a significant proportion of hyperfiltration in patients with T1D based on measured GFR and concluded that estimated GFR cannot replace measured GFR

in T1D patients with hyperfiltration (72). Recently, MacIsaac et al. demonstrated that, in adults with T1D and T2D, estimated GFR by creatinine significantly underestimated early decline in measured GFR (73). There is, thus, a clear need to improve calculation of GFR in the ambulatory setting. We recently demonstrated that iohexol clearance using dried capillary blood spots on filter paper measured GFR accurately in adults with T1D compared to the gold standard method of plasma iohexol measurement (74). This method was also piloted for feasibility in adolescents and adults with T1D (74, 75) and has the potential to be translated to screening for early kidney disease in adolescents with T2D in both clinical and research settings (74).

Novel biomarkers for the prediction of DKD

DKD is characterized by a long, clinically silent period without signs or symptoms of disease. However, while albuminuria and estimated glomerular filtration rate are currently the best means of screening for DKD in adolescents with T2D, there is a need for improved methods to detect early mediators of renal injury. Early detection would improve risk stratification and ultimately prevent initiation and progression to ESRD. Serum and urinary biomarkers that show promise in predicting DKD in adults with T2D are listed in Table 1. Circulating TNF Receptors 1 and 2 are particularly promising and strongly predicted ESRD in adults with T2D with and without proteinuria (76). Rather than examining single biomarkers, improved prediction may also be obtainable with panels of several urinary or serum biomarkers. Looker et al recently examined a broad set of 207 serum biomarkers in 154 Scottish T2D adults with incident cases of progressive GFR decline, and 153 non-progressing controls from the Genetics of Diabetes Audit and Research Tayside Study (GO-DARTS). A panel of 14 of these biomarkers (including FGF-21, SDMA, ADMA, β2-microglobulin, C16-acylcarnitine, and KIM-1) significantly improved upon the predictive performance of rapid progression by clinical data alone, with an increase in the area under the ROC curve from 0.706 to 0.868 (77). Similar analyses are needed in adolescents with T2D.

Urinary proteomics is also a promising method of evaluating DKD risk early in the course of illness (78–81). CKD273, a panel of 273 urinary biomarkers, has shown to improve prediction of macroalbuminuria in individuals prior to an increase in albumin excretion (78–81). Furthermore, the addition of multi-peptide biomarkers to eGFR and albuminuria significantly improved prediction of CKD (80).

Another novel group of biomarkers are gasotransmitters, which include nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S). These gasotransmitters play important roles in the glomeruli for scavenging of reactive oxygen species, blood pressure regulation, and inflammation (82, 83). In diabetes, the bioavailability of gasotransmitters is generally lowered. For instance, deficiency of endothelial nitric oxide synthase (NOS) results in accelerated nephropathy in diabetic mice (84–86) and supplementation of tetrahydrobiopterin, a co-factor of NOS, reduces proteinuria and renal injury in T2D rats (87). Measurements of NO, CO, and H_2S are not routinely available and remain technically challenging due to a relatively short half-life (82). Studies in humans are also needed to determine whether gasotransmitters are important risk factors for progression of DKD.

Novel therapeutic targets

Insulin sensitivity

Insulin resistance leads to important hemodynamic changes in the kidney, including increased sympathetic nervous system tone, hypertension, and accelerated atherosclerosis of the renal microvasculature. We previously demonstrated relationships between measured insulin sensitivity, albuminuria, and eGFR and also found lower odds of albuminuria with greater insulin sensitivity in adolescents with T2D (7). The association between insulin sensitivity and DKD is also increasingly recognized in adults with T2D, with reports demonstrating a cross-sectional relationship between measured insulin sensitivity and albuminuria (88), greater odds of albuminuria in adult T2D males with the highest quartile of HOMA-IR (89), and longitudinal associations between HOMA-IR and incident microalbuminuria over 5-years (90).

While insulin sensitivity can be modified by lifestyle changes (diet and exercise), drugs, such as metformin, have also been examined in renal studies. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) study showed no benefit of an insulin sensitizing strategy on DKD in older adults with coronary artery disease and T2D (91) and the use of metformin in adults with T2D and stage 5 CKD has been associated with a significantly increased risk of all-cause mortality (92). While these studies showed no benefit of insulin sensitization on DKD in T2D, they were conducted in cohorts of older adults with multiple cardiovascular risk factors and longstanding nephropathy who may be less responsive to changes in insulin sensitivity than early DKD in adolescents with T2D. Therefore strategies to improve insulin sensitivity in T2D youth may still be of benefit to renal health and deserve further study.

Uric acid

Serum uric acid is a recognized risk factor for DKD in T2D (93, 94). Patients with T2D have elevated serum uric acid concentrations compared to their non-diabetic peers (95). Moreover, the metabolism of fructose, which is endogenously produced in diabetes from excess glucose via the polyol pathway, is associated with the generation of uric acid from a side chain reaction driven by ATP depletion and purine nucleotide turnover (96). Evidence from animal studies demonstrates that blocking uric acid production protects the kidney from tubulointerstitial injury, which may suggest a causal role for uric acid in the development of DKD (96). In an Italian cohort of T2D adults with normal kidney function and without overt proteinuria, the risk of CKD during a 5 year follow-up was significantly higher in participants with hyperuricemia compared with those without (93). In adults with T2D and DKD, serum uric acid was also found to predict progression of established DKD (94). From a renal therapeutic perspective, a post hoc analysis of the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Trial found that lowering serum uric acid levels with losartan, which reduces serum uric acid levels by facilitating urinary uric acid excretion, accounted for 20% of the renoprotective benefit of this medication (97). More direct uric acid lowering with xanthine oxidase inhibitors, such as allopurinol, significantly reduces proteinuria in T2D patients and macroalbuminuria (98) and may also help maintain stable renal function and reduce

cardiovascular risk in patients with T2D (99, 100). Studies examining the relationships between serum uric acid and DKD in adolescents with T2D are needed to determine if uric acid plays a role in the pathophysiology of pediatric T2D. To determine whether uric acid lowering translates into renal or cardiovascular protective effects, the Preventing Early Renal Function Loss in Diabetes (PERL) study is an on-going multi-center, double-blind, randomized clinical trial of allopurinol in individuals with T1D and either albuminuria or renal functional decline (101). If PERL produces promising results, similar studies should be considered in adolescents and young adults with T2D.

Vasopressin

Arginine vasopressin (AVP) plays an essential role in regulation of volume status and exerts important renal and cardiovascular effects in health and disease. It is recognized that AVP infusion induces hypertension, glomerular hyperfiltration, and albuminuria (102–104). Unfortunately, measuring AVP is technically difficult due to its relatively small size and short half-life. Copeptin is a more stable peptide derived from the same precursor molecule as AVP, is accepted as a surrogate marker for AVP, and is useful in the assessment of fluid and osmotic status in various diseases. AVP concentrations are higher in adults with T2D compared with healthy counterparts (105, 106). High concentrations of plasma AVP are known to preferentially stimulate vasopressin V1a receptors (107), which may contribute to the cardiovascular and renal complications associated with diabetes. For example, Fenske et al. recently reported that copeptin was strongly associated with cardiovascular events and mortality in adults with T2D (107). Similar findings were also demonstrated by Riphagen et al. who showed that copeptin correlated with cardiovascular and all-cause mortality in adults with T2D in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC-31) study (108). In adults with T2D, copeptin has also been associated with declining GFR in the type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril (DIABHYCAR) (109), and ZODIAC-33 studies (110). To our knowledge, the association between copeptin and renal health in youth with T2D has yet to be examined. The vasopressin system is not only a modifiable risk factor, but also a promising therapeutic target with the recent availability of vaptans (vasopressin receptor antagonists). Vaptans are generally well-tolerated, with most commonly reported adverse effects including dry mouth, thirst and increased daytime urination (111).

ACE2 and neprilysin

Another important system in DKD is the renin-angiotensin-aldosterone system (RAAS). However, RAAS inhibition does not halt or delay progression of DKD in T2D (112–114) as effectively as it does in T1D (113). While a primary prevention study failed to demonstrate benefit of RAAS inhibitors (2) and another showed harm with dual RAAS blockade (3), the identification of angiotensin-converting enzyme 2 (ACE2) has changed our understanding of RAAS and introduced potential new therapeutic targets (115). ACE2 is expressed in most tissues, but especially abundant in the kidney (116) and cleaves the C-terminal amino acid of Angiotensin II to generate the peptide Angiotensin 1-7, which is thought to provide renoprotection by counteracting the adverse effects of Angiotensin II (117). Angiotensin 1-7 is also thought to reduce oxidative stress, inflammation, and lipotoxicity (118). Diabetic animal models are associated with Angiotensin II over-activity (119, 120) and studies with

downregulation of tubular ACE2 found significant albuminuria and tubular injury (121, 122). Furthermore, ACE2 activity at the podocytes can attenuate the development of DKD (123), suggesting a potential mechanism to counteract diabetes-associated Angiotensin II over-activity (119, 120). In fact, DKD is associated with reduced tubular ACE2 expression (124) and ACE2 activity is associated with glycemic control and glomerular filtration rate (GFR) in adults with DKD (125). For these reasons, studies have investigated ACE2 as a potential therapeutic target using recombinant ACE2 and Mas receptor modulators to diminish DKD progression, with promising preliminary results (126–130).

A system strongly related to RAAS is the natriuretic peptide (NP) system that counter-regulates the RAAS. Neprilysin is an enzyme responsible for degradation of NPs (131). Neprilysin inhibitors (NEPi) lead to natriuresis, vasodilatation, and reductions in both intraglomerular pressure and proteinuria (132, 133). The beneficial renal effects of NEPi may be enhanced when combined with RAAS blockade, which led to the development of combined NEPi/RAASi agents. While no large-scale human trials have been conducted with NEPi or NEPi/RAASi in a CKD cohort to date, animal models show promising results. For instance, in a 5/6 nephrectomy model (CKD animal model with unilateral nephrectomy and either partial infarction or amputation of the poles of the remaining kidney), AVE7688, a vasopeptidase blocking ACE and NEP, increased renal synthesis of nitric oxide, decreased synthesis of endothelin-1, and increased tubular ANP release, leading to with reduced renal vasoconstriction, proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis (134). LCZ696, a combined angiotensin-neprilysin inhibitor, was shown to be superior to enalapril in reducing the risks of death and hospitalization for heart failure in adults with and without diabetes in the PARADIGM-HF study (135, 136). Renal outcome studies using this emerging class are not yet available.

Sodium glucose co-transporter 2

Another important emerging therapeutic area relates to sodium glucose co-transporter 2 (SGLT2) inhibition. This class of agents has a strong mechanistic basis for renal protection in both T2D and T1D. In adults with T1D, SGLT2 inhibition with empagliflozin significantly attenuates renal hyperfiltration, likely by restoring the altered tubular-glomerular feedback mechanism leading to hyperfiltration (137). SGLT2 inhibition blocks proximal tubular glucose and sodium reabsorption, which leads to increased sodium delivery to the macula densa, thereby reducing GFR and renal blood flow (RBF) via afferent arteriolar vasoconstriction (137). Furthermore, in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG RENAL) trial, empagliflozin was well-tolerated, reduced HbA1c in adults with T2D and CKD, and exerted important blood pressure and anti-proteinuric effects in patients with and without DKD (138). Importantly, the EMPA-REG OUTCOME trial, with 7000 individuals from 42 countries observed for a median duration of 3.1 years, recently reported that empagliflozin is the first glycemic lowering therapy to reduce a composite cardiovascular endpoint (defined as time to first occurrence of either CV death, or non-fatal myocardial infarction or non-fatal stroke). To our knowledge, there are no studies demonstrating attenuation of hyperfiltration in T2D with SGLT2 inhibition, but it is likely that SGLT2 inhibitors will affect the tubular-glomerular feedback mechanisms similarly to what has been observed in T1D.

Conclusion

The increasing prevalence of T2D worldwide has led to a concomitant rise in DKD (4, 56). Left untreated, patients with DKD have a high risk of progressing to ESRD and dialysis – a significant public health burden (4). Particularly worrisome is the decreasing age of onset of T2D and the presence of DKD even at time of diagnosis. This review examines the current literature and data addressing novel biomarkers and potential therapeutic targets in early DKD in adolescents with T2D. Longitudinal human research is required to develop improved methods of measuring renal function in adolescents with T2D, and to investigate the effect of novel pharmacotherapy on long-term clinical outcomes.

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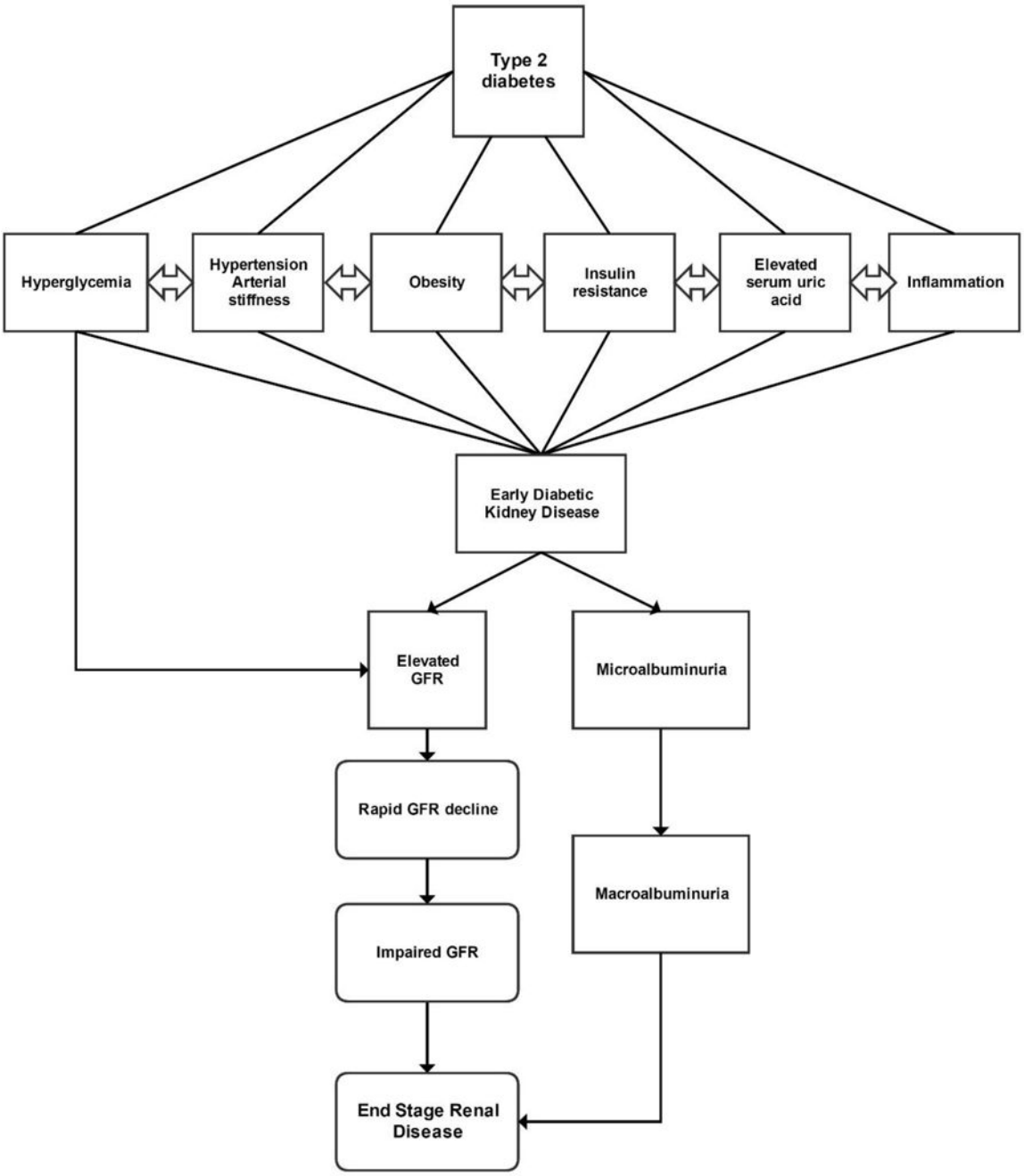

Figure 1.
Risk factors for diabetic nephropathy in youth with type 2 diabetes

Table 1

Serum and urinary biomarkers of DKD

	Biomarker	Reference
Promising serum biomarkers		
	TNF receptor 1 and 2	(139)
	Kidney injury molecule-1	(77, 140)
	Fibroblast growth factor 21 and 23	(77, 141)
	Symmetric dimethylarginine (SDMA)	(77)
	Asymmetric dimethylarginine (ADMA)	(77)
Promising urinary biomarkers		
	Neutrophil gelatinase associated lipocalin (NGAL)	(142, 143)
	Metalloproteinases	(144)
	N-acetyl-beta-glucosaminidase	(145, 146)
	Nephrin	(147, 148)
	Alpha 1-microglobulin	(149, 150)