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Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment

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ABSTRACT

An absolute, supraphysiologic elevation in GFR is observed early in the natural history in 10%–67% and 6%–73% of patients with type 1 and type 2 diabetes, respectively. Moreover, at the single-nephron level, diabetes-related renal hemodynamic alterations—as an adaptation to reduction in functional nephron mass and/or in response to prevailing metabolic and (neuro)hormonal stimuli—increase glomerular hydraulic pressure and transcapillary convective flux of ultrafiltrate and macromolecules. This phenomenon, known as glomerular hyperfiltration, classically has been hypothesized to predispose to irreversible nephron damage, thereby contributing to initiation and progression of kidney disease in diabetes. However, dedicated studies with appropriate diagnostic measures and clinically relevant end points are warranted to confirm this assumption. In this review, we summarize the hitherto proposed mechanisms involved in diabetic hyperfiltration, focusing on ultrastructural, vascular, and tubular factors. Furthermore, we review available evidence on the clinical significance of hyperfiltration in diabetes and discuss currently available and emerging interventions that may attenuate this renal hemodynamic abnormality. The revived interest in glomerular hyperfiltration as a prognostic and pathophysiologic factor in diabetes may lead to improved and timely detection of (progressive) kidney disease, and could provide new therapeutic opportunities in alleviating the renal burden in this population.

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Driven by the ever-increasing prevalence of diabetes, diabetic kidney disease (DKD) has become the most common cause of CKD, leading to ESRD, cardiovascular events, and premature death in developed and developing countries.[1] In order to reduce the onset and progression of DKD, current management focuses on prevention, early identification, and treatment. Diabetes and nephrology guidelines advocate strict glycemic and BP targets, the latter for which renin-angiotensin system (RAS) inhibitors are recommended in diabetes patients with[2] and without[3] albuminuria. Despite increased efforts that stabilized incidence rates for ESRD attributable to DKD in the United States over the last 5 years, the number of patients with renal impairment due to diabetes is still increasing.[4] Therefore, improved and timely strategies are needed.

In addition to albuminuria, reduced GFR is a pivotal marker in predicting the risk for ESRD and renal death in diabetes, whereas the role of increased GFR is uncertain. In the classic, five-stage, proteinuric pathway of DKD, the initial phase is characterized by an absolute, supraphysiologic increase in whole-kidney GFR (*i.e.*, the sum of filtration in all functioning nephrons) (Figure 1). This early clinical entity, known as glomerular hyperfiltration, is the resultant of obesity and diabetes-induced changes in structural and dynamic factors that determine GFR.[5] Reported prevalences of hyperfiltration at the whole-kidney level vary greatly: between 10% and 67% in type 1 diabetes mellitus (T1DM) (with GFR values up to 162 ml/min per 1.73 m^2), and 6%–73% in patients with type 2 diabetes (T2DM) (up to 166 ml/min per 1.73 m^2, Table 1). In general, GFR increases by about 27% and 16% in recently diagnosed patients with T1DM[6] and T2DM,[7] respectively. The prevailing hypothesis is that hyperfiltration in diabetes precedes the onset of albuminuria and/or decline in renal function, and predisposes to progressive nephron damage by increasing glomerular hydraulic pressure (P_{GLO}) and transcapillary convective flux of ultrafiltrate and, although modestly,

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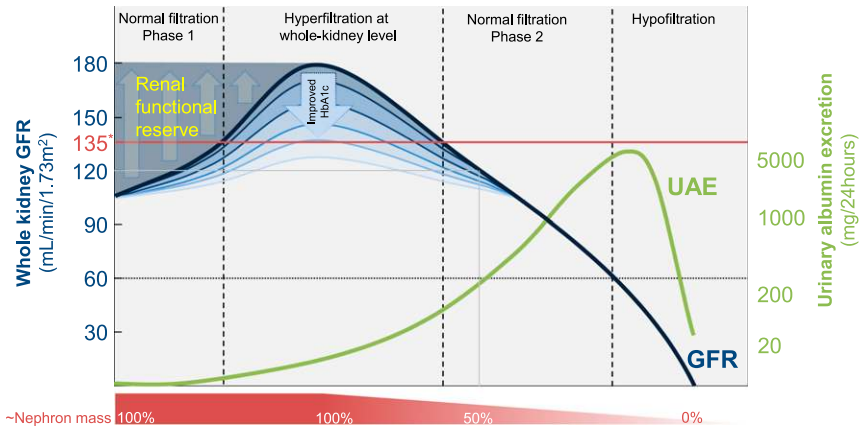


Figure 1. Classic course of whole-kidney GFR and UAE according to the natural (proteinuric) pathway of DKD. Peak GFR may be seen in prediabetes or shortly after diabetes diagnosis, and can reach up to 180 ml/min in the case of two fully intact kidneys. Strict control of HbA_{1c} and initiation of other treatments (such as RAS inhibition) mitigate this initial response. Two normal filtration phases can be encountered, in which GFR may be for instance 120 ml/min (indicated with the gray line): one at 100% of nephron mass and one at approximately 50% of nephron mass. Thus, whole-kidney GFR may remain normal even in the presence of considerable loss of nephron mass, as evidenced by a recent autopsy study.[121] Assessing renal functional reserve and/or UAE may help identify the extent of subclinically inflicted loss of functional nephron mass. *Whole-kidney hyperfiltration is generally defined as a GFR that exceeds approximately 135 ml/min, and is indicated with the red line. Heterogeneity of single-nephron filtration rate and nonproteinuric pathway[122] of DKD are not illustrated.

macromolecules (including albumin). Furthermore, increased GFR in single remnant nephrons—to compensate for reduced nephron numbers[8,9] and/or caused by stimuli of the diabetes phenotype—is proposed to accelerate renal function decline in longer-standing diabetes.

This review summarizes proposed factors that underlie hyperfiltration in diabetes, and addresses evidence of this phenomenon as predictor and pathophysiologic factor in DKD. Furthermore, we discuss lifestyle and (emerging) pharmacologic interventions that may attenuate hyperfiltration.

DEFINITION AND MEASUREMENT

"Whole-Kidney" Hyperfiltration

Although a generally accepted definition is lacking, reported thresholds to define hyperfiltration vary between 130 and 140 ml/min per 1.73 m^2 in subjects with two functioning kidneys,[10] which corresponds to a renal function that exceeds two SD above mean GFR in healthy individuals.[11] Notably, use of any set GFR cutoff does not consider differences between sexes and distinct ethnic populations,[10] nephron endowment at birth,[12] and age-related GFR decline.[10,13] Identification of hyperfiltration in clinical practice and systematic studies is complicated by intra- and interday GFR fluctuations,[14,15] and the inaccuracy of available serum creatinine–based GFR estimates.[16] As such, the Cockroft–Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration 2009 equations systematically underestimate GFR in diabetes, and progressively more so with increasing GFR.[16] This seems due to changes in tubular creatinine secretion in the setting of obesity, hyperglycemia, and hyperfiltration, although high glucose concentrations also lead to overestimation of serum creatinine when the Jaffe reaction is used.[16] eGFR on the basis of serum cystatin C is suggested to more accurately reflect renal function in patients with diabetes and normal or elevated GFR.[17,18] Nevertheless, renal clearance techniques using inulin, or its more widely used alternative sinistrin, are required for gold standard measurement of GFR.[19] However, because inulin and sinistrin require labor-intensive analysis, alternative well recognized, although less accurate, exogenous filtration markers across GFR values are widely used in clinical practice and research, such as (^{125}I-labeled) iothalamate, iohexol, ^{51}Cr-labeled ethylenediaminetetra-acetic acid, and ^{99m}Tc-labeled diethylenetriaminepenta-acetic acid.[19,20]

"Single-Nephron" Hyperfiltration

The definition of hyperfiltration at the whole-kidney level disregards conditions in single nephrons, for which two distinct (frequently co-occurring) elements seem to be involved. First, in the natural history of DKD, with irreversible damage to progressively more glomeruli, remnant nephrons undergo functional and structural hypertrophy (glomeruli and associated tubules), thereby striving to maintain whole-kidney filtration and reabsorption within the normal range.[21] Second, and regardless of renal mass, metabolic and (neuro)hormonal stimuli that prevail in diabetes and/or obesity (as discussed below) enhance filtration in single nephrons, even when whole-kidney GFR does not exceed 130–140 ml/min per 1.73 m^2 (Figure 1). Given these considerations, hyperfiltration has also been defined as a filtration fraction[11,22] (FF; the ratio between GFR and effective renal plasma flow [ERPF]) above 17.7%±2.8%, *i.e.*, the mean±SD in healthy 22–25–year-old humans.[23] In support of such a definition, a mean FF of 24% is observed in adolescents with uncomplicated T1DM and a GFR of 178 ml/min per 1.73 m^2, whereas FF is 17% in those with a GFR of 111 ml/min per 1.73 m^2.[24] ERPF is measured using para-aminohippuric acid, radioiodine-labeled hippuran, or ^{99m}Tc-labeled mercaptoacetyltriglycine, which are removed from the circulation during a single pass through the kidney by approximately 90%,[25] 75%,[25] or 55%,[26] respectively. Whether FF is a valid approximation of P_{GLO} is subject to debate, as the latter can only be directly measured by micropuncture. However, in humans there is no alternative,[27] other than estimation with Gomez equations (using measured GFR and ERPF, and total protein).[28,29] Some authors propose that a

Table 1. Prevalence studies of hyperfiltration in diabetes

Study Author(s) and Year	*N*	Diabetes Duration			Baseline HbA_{1c}, %			GFR Method	GFR, ml/min per 1.73 m^2			HF Threshold, ml/min per 1.73 m^2	Prevalence of HF, %
		All	HF	NH	All	HF	NH		All	HF	NH		
T1DM													
Kalk *et al.* (1990)[131]	127	8	6		10.8			^{51}Cr-EDTA	129	162	107	135	34
Azevedo and Gross (1991)[132]	21		5	7		10.1	10.7	^{51}Cr-EDTA		156	107	134	48
Marre *et al.* (1992)[133]	50		12	11		9.1	8.2	^{51}Cr-EDTA		148	111	125	42
Cotroneo *et al.* (1998)[134]	177							^{51}Cr-EDTA				135	56
Caramori *et al.* (1999)[135]	33	7						^{51}Cr-EDTA		155	108	134	63
Dahlquist *et al.* (2001)[136]	60	29						Inulin				125	50
Amin *et al.* (2005)[137]	308	5			10.4			Inulin[b]				125	67
Vervoort *et al.* (2005)[138]	54	5	8	9		8.4	8.3	Inulin	121	143	114	130	24
Steinke *et al.* (2005)[139]	107	8			8.6			Inulin	142			130	63
Ficociello *et al.* (2009)[67]	426	14	12	14		8.6	8.1	eGFR		155	122	134 (M)/149 (F)[a]	24
Thomas *et al.* (2012)[68]	2318	18	11	19		8.8	8.2	eGFR				125	10
Bulum *et al.* (2013)[140]	313							eGFR				125	12
T2DM													
Palmisano and Lebovitz (1989)[141]	72							^{125}I-iothalamate				140	25
Lebovitz and Palmisano (1990)[142]	71							^{125}I-iothalamate				140	35
Marre *et al.* (1992)[133]	19		13	6		6.8	7.6	^{51}Cr-EDTA		134	108	125	32
Norwack *et al.* (1992)[143]	16	0.5			6.5			Inulin	133			141	44
Vora *et al.* (1992)[144]	110							^{51}Cr-EDTA				140	16
Gragnoli *et al.* (1993)[145]	163							^{99m}Tc-DTPA				139	6
Silveiro *et al.* (1993)[146]	71		7	6		10.4	9.4	^{51}Cr-EDTA		147	110	137.1	21
Bruce *et al.* (1994)[147]	15							^{51}Cr-EDTA	166			140	73
Lee *et al.* (1995)[148]	284							^{51}Cr-EDTA				140	23
Silveiro *et al.* (1996)[63]	32							^{51}Cr-EDTA				137	40
Keller *et al.* (1996)[149]	85	1			9.1			Inulin	136			131	58
Chaiken *et al.* (1998)[150]	194							^{125}I-iothalamate				140	17
Guizar *et al.* (2001)[151]	28	0.3			6.2			^{99m}Tc-DTPA	140			140[b]	72
Premaratne *et al.* (2005)[152]	662							^{99m}Tc-DTPA				130	7/17[d]
Jin *et al.* (2006)[153]	93		11	7		8.1	7.0	Iohexol		141	99	Age-adjusted[c]	17
Ruggenenti *et al.* (2012)[62]	600	7	6	7	6.2	6.7	6.1	Iohexol	101	132	96	120	15
Guo *et al.* (2016)[154]	3301							eGFR				138	12
T1DM and T2DM													
Zhao *et al.* (2015)[155]	3492		8	8		9.7	9.0	^{99m}Tc-DTPA		140	88	129	10

HF, hyperfiltration; NH, nonhyperfiltration; M, males; F, females; ^{51}Cr-EDTA, chromium 51–labeled EDTA; ^{99m}Tc-DTPA, ^{99m}Tc-labeled diethylenetriaminepenta-acetic acid.

[a]HF definition was sex-specific.

[b]HF was additionally defined as <10% increase in GFR after an acute protein load.

[c]HF was defined as GFR greater than the mean GFR + 1.96 SD of control subjects, after adjustment for age.

[d]Correction for age-related GFR decline increased HF prevalence from 7% to 17%.

stress test, which is capable of exploiting the entire filtration capacity of the kidneys (known as the renal functional reserve; *i.e.*, by means of a high-protein load, or infusion of amino acids or dopamine), could be a significant tool to identify a hyperfiltering state in patients with whole-kidney GFR within normal range, assuming that a preexisting elevation of P_{GLO} and ERPF will prevent a rise in GFR (Figure 2).[30,31] However, utility of such a diagnostic measure remains uncertain, as variability of renal functional reserve testing makes an impaired GFR response to a stimulus difficult to identify and hard to interpret.

PATHOGENESIS OF HYPERFILTRATION IN DIABETES

Pathogenesis of hyperfiltration in diabetes is complex, comprising numerous mechanisms and mediators, with a prominent role for hyperglycemia and distorted insulin levels,[32] especially in early diabetes[33] and prediabetes.[34] As such, prevalence of diabetes-related hyperfiltration may have been dropped due to earlier diagnosis and modern day stricter control of hyperglycemia and other factors (*e.g.*, angiotensin II by means of RAS blockade). For example, reducing glycated hemoglobin A_{1c} (HbA_{1c}) from 10% to 7%, which could be considered adequate glycemic control,[35] normalized measured GFR from 149 to 129 ml/min per 1.73 m^2 (16% reduction) in patients with T1DM on insulin pump therapy, whereas no effect on GFR was observed in the control group that continued conventional insulin treatment without changes in HbA_{1c}.[36] Notably, independent of diabetes and glucose levels,[37] body weight also augments GFR (by about 15% in obese[37] to about 56% in severely obese nondiabetic subjects[38,39]). Thus, especially in T2DM, hyperfiltration likely develops after and on top of body weight–induced increases in GFR, although such longitudinal data are not available. The mechanisms of hyperfiltration, which may overlap and act in concert, are briefly discussed at ultrastructural, vascular, and tubular level.

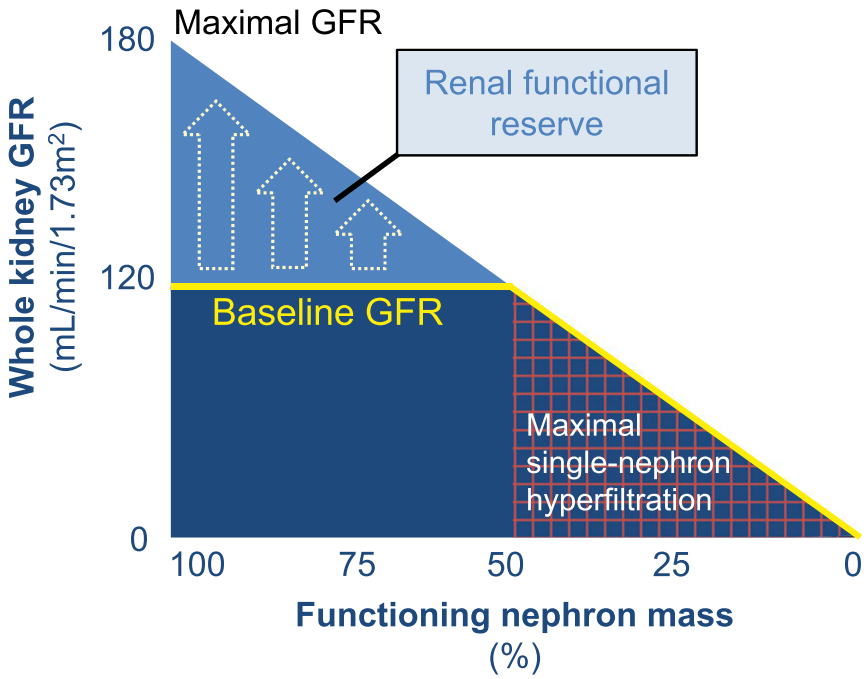


Figure 2. Schematic representation of renal functional reserve. Renal functional reserve is defined as the capacity of the kidney to compensate or increase its function in states of demand (*e.g.*, high protein or fluid intake, pregnancy) or disease (*e.g.*, diabetes, CKD).[31] In early diabetes, when nephron mass is still >50%, renal functional reserve may be reduced due to prevailing metabolic and (neuro)hormonal factors that increase baseline GFR. In later stages, additional renal hemodynamic adaptations occur in response to reduced renal mass, leading to continuous maximal use of glomerular filtration capacity.

Ultrastructural Changes

From the onset of diabetes, the kidneys grow large due to expanded nephron size (particularly hypertrophy of the proximal tubule).[32,40] This phenomenon is most likely caused by various cytokines and growth factors in response to hyperglycemia,[41] although obesity may also independently contribute to nephromegaly.[11,42] Although increased kidney size[36,43] and filtration surface area per glomerulus[44] have been linked to hyperfiltration, it has been proven difficult to separate cause from effect.[40] Some have suggested that (compensatory) hypertrophy occurs *as a result* of hyperfiltration.[45] However, in animal studies, hypertrophy precedes hyperfiltration.[41] Inhibition of the rate-limiting enzyme ornithine decarboxylase to reduce early diabetic tubular hypertrophy and—likely subsequent—proximal hyperreabsorption of sodium (see below) diminishes hyperfiltration in direct proportion to the effect on kidney size in diabetic rats.[46] Because tubular growth reverses slowly, and normalization of kidney size may not be achieved in patients with diabetes even after strict glycemic control, hyperfiltration could endure due to persistent tubular enlargement and changes in tubular functions.

Vascular Theory

According to the "vascular theory," hyperfiltration results from imbalance of vasoactive humoral factors that control pre-and postglomerular arteriolar tone leading to hyperfiltration, as depicted in Figure 3.[8,32] Preferential sites of action of these factors are derived from infusion or blockade studies in preclinical models and humans, in which reduced FF is frequently related to a vasodilatory effect on the efferent arteriole or vasoconstrictive effect on the afferent arteriole. However, FF reduces also with

proportional decreases in efferent and afferent arteriolar resistance (as the former decreases FF more than the latter increases FF), which denotes that changes in FF are not necessarily indicative for selective alteration in segmental vascular resistance (Supplemental Figure 1).[47] As various vasoactive mediators are released or activated after a meal, they may be effectors in postprandial hyperfiltration (Figure 3).[48] In addition, amino acids from digested proteins may directly[49,50] and indirectly[48] increase tubular reabsorption of sodium and subsequently inactivate tubuloglomerular feedback (TGF; see below).

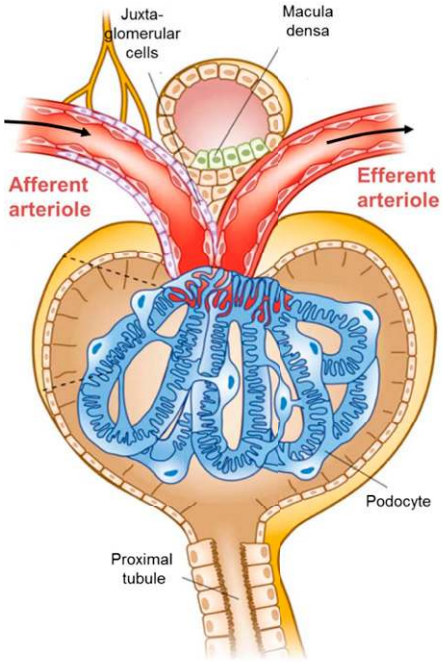
Tubular Theory

The "tubular theory" of hyperfiltration describes diabetes-related abnormalities in the close interaction between the glomerulus and tubule. It proposes that enhanced proximal tubular sodium (and glucose) reabsorption, paralleled by tubular growth[32] and upregulation of sodium-glucose cotransporters (SGLTs) and sodium-hydrogen exchanger (NHE) 3, leads to a reduction in afferent arteriolar resistance and increase in single-nephron GFR through inhibition of TGF (Figure 3).[32,42,51] The raised intrarenal pressure in obese patients—due to increased intra-abdominal pressure and accumulation of peri-renal fat—compresses the thin loops of Henle, which may add to enhanced tubular sodium reabsorption.[52–54] Finally, diabetes-associated tubular hyperplasia and hypertrophy[32] and proximal tubular hyper-reabsorption reduce intratubular pressure and hydraulic pressure in Bowman's space, which further perpetuates hyperfiltration by increasing the net hydraulic pressure gradient.[55,56]

CLINICAL SIGNIFICANCE OF HYPERFILTRATION IN DIABETES

Elucidating the significance of hyperfiltration as an independent renal risk factor in diabetes is complicated by the complex multifactorial etiology of DKD, and the lack of dedicated studies that assess the influence of sustained or altered whole-kidney hyperfiltration and FF on long-term renal outcome. Hyperfiltration *per se* does not seem to fully explain adverse renal outcome, as the risk for ESRD in transplant donors (in which

Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se*
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals)



Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin-II
Thromboxane A2
Endothelin-1 (ETA receptor)
Reactive oxygen species

Figure 3. Schematic (net) effect of factors implicated in the pathogenesis of glomerular hyperfiltration in diabetes. Several vascular and tubular factors[32,48,123–126] are suggested to result in a net reduction in afferent arteriolar resistance, thereby increasing (single-nephron) GFR. Effects of insulin *per se* seem to depend on insulin sensitivity.[96,97] A net increase in efferent arteriolar resistance—leading to increased GFR—is proposed for other vascular factors.[32,42,71,124,127] Growth hormone[128] and insulin-like growth factor-1[129] likely increase filtration by augmenting *total* renal blood flow, without specific arteriolar preference. Glucagon and vasopressin seem to (principally) act through TGF.[48] Intrinsic defects of electromechanical coupling or alterations in signal transduction in afferent arterioles may impair vasoactive responses to renal hemodynamic (auto)regulation.[32] Augmented filtration by increases in the ultrafiltration coefficient, and net filtration pressure *via* reduction in intratubular volume and subsequent hydraulic pressure in Bowman's space are not depicted. Several vascular factors may be released or activated after a (high-protein) meal (*e.g.*, nitric oxide, cyclooxygenase-2 prostanoids, angiotensin II),[48,50,130] whereas TGF becomes (further) inhibited, through increased amino acid- (and glucose) coupled sodium reabsorption in the proximal tubule[49,50] and/or increased glucagon/vasopressin-dependent sodium reabsorption in the thick ascending limb.[48] These changes may collectively play a part in postprandial hyperfiltration. COX-2, cyclooxygenase-2; ETA, endothelin A receptor.

single-nephron GFR is typically increased by about 60%–70%)[57] is very low.[58] However, it may be suggested that the stimulus and/or prevailing diabetes play a part in the pathogenesis of hyperfiltration-induced renal damage. As such, an evaluation of 52,998 living kidney donors revealed that non-insulin-dependent diabetes was among the strongest predictors of developing ESRD after 15-years of follow up (hazard ratio, 3.01; 95% confidence interval, 1.91 to 4.74).[59] To date, studies that report on the effects of whole-kidney level hyperfiltration in diabetes are observational in nature, whereas the clinical significance of single-nephron hyperfiltration in all phases of DKD is best deduced from RAS blockade trials. Finally, a potential pathophysiologic role of postprandial hyperfiltration in DKD is suggested in small-sized studies. We will discuss the significance of diabetic hyperfiltration using this somewhat artificial distinction.

Whole-Kidney Hyperfiltration and Renal End Points: Observational Studies

Several epidemiologic studies in diabetes report associations between supraphysiologic GFR in diabetes and all-cause mortality.[60,61] Furthermore, longitudinal cohort studies of 3–18 years' duration show that GFR declines more rapidly in patients with T1DM and T2DM with whole-kidney hyperfiltration compared with those with normal GFR at baseline.[34,62–64] However, as GFR remained in the normal range at end of follow-up (*i.e.*, ≥100 ml/min per 1.73 m^2), it is unclear whether these observations indicate (pharmacologic) resolution of hyperfiltration (*i.e.*, restoration of renal functional reserve), or loss of nephron mass. The latter is suggested in a recent 6-year observational cohort study, in which rapid eGFR decline was associated with baseline hyperfiltration and renal impairment in 509 patients with T1DM.[65]

Additionally, numerous studies reported on the association of whole-kidney hyperfiltration with onset and progression of the surrogate renal end point albuminuria (Table 2). In a systematic review and meta-analysis of ten cohort studies involving 780 patients with T1DM, followed for a mean of 11.2 years,[66] the pooled odds for developing albuminuria in patients with measured whole-kidney hyperfiltration at baseline was 2.71 (95% confidence interval, 1.20 to 6.11). In contrast, other large-sized studies that estimated GFR did not detect such an association.[67,68] Moreover, several studies suggest that the absence of whole-kidney hyperfiltration in T1DM has a negative predictive value of approximately 95% for albuminuria development.[69,70] In a *post hoc* analysis of 600 patients with T2DM, patients with persistent measured hyperfiltration, compared with those with normofiltration at inclusion or in whom hyperfiltration was ameliorated by metabolic and BP control at 6 months, were more likely to develop microalbuminuria or macroalbuminuria over a follow-up of 4 years (hazard ratio, 2.23; 95% confidence interval, 1.1 to 4.3).[62] These observations were maintained even after adjustment for various risk factors, including HbA_{1c}, BP, and duration of diabetes. However, other reported series in T2DM, which were either smaller-sized or used eGFR, are not in line with these results (Table 2).

Despite suggestive evidence that whole-kidney hyperfiltration could contribute to DKD development and progression in T1DM and perhaps T2DM, interpretation of the data is hampered by variations in metabolic control, BP, diabetes duration, and other confounding factors, as well as potential publication bias. To date, no prospective studies with adequate measured and hard end points have investigated the renoprotective potential of controlling early hyperfiltration.

Single-Nephron Hyperfiltration and Renal End Points: RAS Blockade Trials

As angiotensin II induces a net increase in postglomerular resistance,[71] reducing its action with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ARB) lowers FF and P_{GLO}.[72] Consequently, RAS blockers are known to variably increase serum creatinine, which may raise up to 30% in patients with CKD in the first month after treatment initiation, and is generally reversible after drug discontinuation.[73] Furthermore, 3-week enalapril treatment reduced GFR and FF in 11 adolescents with uncomplicated T1DM and whole-kidney hyperfiltration.[24]

Pivotal trials in patients with T1DM and T2DM, which indicated that RAS blockade reduces the rate of developing albuminuria and hard renal end points, independent from BP lowering, have placed these drugs at the cornerstone of renoprotective management.[74] Notably, a greater initial fall in eGFR portends a slower subsequent decline in renal function in patients with T2DM assigned to the ARB losartan (Figure 4), which supports the notion that reducing single-nephron hyperfiltration ameliorates DKD risk.[75] However, as there is a close relationship between P_{GLO} and urinary albumin excretion (UAE),[76] and RAS blockade benefits both renal risk factors, the independent contribution of each to long-term renal preservation remains unknown.

Postprandial Hyperfiltration and Renal End Points: Speculative Studies

The pathophysiologic role of meal-induced increases in (single-nephron) GFR, known as postprandial hyperfiltration, in the onset or progression of CKD is a re-emerging field of study, especially in the context of high-protein diets that aim to induce weight-loss in obesity and T2DM. As such, in a 7-day crossover study in healthy young men, high-protein intake (2.4 g/kg per day) compared with normal protein intake (1.2 g/kg per day) increased measured GFR, FF, and 24-hour UAE.[77] As humans largely reside in the postprandial state, the excessive and prolonged metabolic and hormonal disturbances occurring after meal ingestion in diabetes could, in theory, unfavorably influence kidney function, and predispose to renal damage. Interestingly, a blunted rise in GFR after amino acid infusion or protein loading in the presence of a RAS inhibitor has been widely described,

Table 2. Observational studies on the association of hyperfiltration and albuminuria progression or nonprogression in diabetes

Study Author(s) and Year	Baseline MA Status	N			Follow-Up, yr	Baseline HbA_{1c}, %			GFR Method	Baseline GFR, ml/min per 1.73 m^2			HF Threshold, ml/min per 1.73 m^2[2a]	Prevalence of HF, %		Risk Estimate	Summarized albuminuria risk
		All	P	NP		All	P	NP		All	P	NP		P	NP		
T1DM																	
Mogensen (1986)[156a]	N	12									166	138					↑
Lervang *et al.* (1988)[157]	N	29	8	21	18#		9.3*	7.2*	Inulin		142#	147#				OR, 0.67*	=
Azevedo and Gross (1991)[132]	N	21	0	21	3.4	10.4			^{51}Cr-EDTA				134				=
Lervang *et al.* (1992)[158]	N	34	17	17	12#		10.8*	9*	^{51}Cr-EDTA	~136#	134#	137#				OR, 0.45*	=
Rudberg *et al.* (1992)[70]	N	53	18	35	8	11.8			Inulin	135	~150	~130	119				↑
Bognetti *et al.* (1993)[159]	N	38	7	31	2.5	8.8			^{51}Cr-EDTA				135	43	52	OR, 0.89	=
Chiarelli *et al.* (1995)[69]	N	46	8	38	10	9.7	12.2	9.5	^{51}Cr-EDTA	~142	~169		140	87	42	OR, 9.97*	↑
Yip *et al.* (1996)[160]	N	50	7	43	9.6	~9.9			^{51}Cr-EDTA	~135			135	57	49	OR, 1.00*	=
Caramori *et al.* (1999)[135]	N	33	3	30	8.4	9.9	11.4*	9.9*	^{51}Cr-EDTA				134	100	60	OR, 4.95*	↑
Dahlquist *et al.* (2001)[136]	N	60	19	41	8	11.9	12.2	11.8	Inulin	~135	~139	129	125	84		OR, 3.81	↑
Amin *et al.* (2005)[137]	N	273	30	243	10.9	~9.9#	11.4	9.7	Inulin[b]	~142	167	139	125	97	64	OR, 16.44*	↑
Steinke *et al.* (2005)[139]	N	107[c]	8	99	5	~8.5	9.2	8.4	Inulin	~144	163	143	130	88	61	OR, 4.48*	↑
Zerbini *et al.* (2006)[161]	N	146	27	119	9.5	~9.2	9.8	9	^{51}Cr-EDTA	~120	122	118				OR, 2.01*	=
Ficociello *et al.* (2009)[67]	N	426	94	332	15	~8.2			eGFR	~130			134 (M)/149 (F)[d]	21	25	HR, 0.8	=
Thomas *et al.* (2012)[68]	N	2318	162	2156	5.2#	~8.3	9.2	8.2	eGFR				[e]			[e]	=
Mogensen and Christensen (1984)[162]	N/MA	43	16	27	10.4		6.9*	7.4*	^{125}I-iothalamate		158	134				OR, 33.12*	↑
Mogensen and Christensen (1985)[163]	N/MA	31	9	22	11.7				^{125}I-iothalamate	140						R 0.78[f]	↑
Jones *et al.* (1991)[164]	N/MA	50	6	44	4.7	~9.9			^{51}Cr-EDTA				135				=
Bangstad *et al.* (2002)[165]	N/MA	18	3	15	8	10.1			Inulin	143	150	143					↑/=
Mathiesen *et al.* (1997)[166]	MA	40	14	26	5	~8.7	9.2	8.4	^{51}Cr-EDTA	~120	122	115					=
Couper *et al.* (1997)[167]	MA	59	15	44	2.3#	~9.9	10.8	9.7	^{99m}Tc-DTPA		"no difference"						=
Amin *et al.* (2005)[137]	MA	35	9	26	10.9	10.8#	12.1	10.3	Inulin[b]	134	132	135	125	57	72	OR, 0.79	=
T2DM																	
Silveiro *et al.* (1996)[63]	N	32	9	23	5				^{51}Cr-EDTA	~128	123	129	137	43	40	OR, 1.13	=
Nelson *et al.* (1996)[7]	N	24			4				Iothalamate								=
Murussi *et al.* (2006)[168]	N	50	14	36	9.3	~6.9	7.5	6.7	^{51}Cr-EDTA	121	128	118	137	38	22	OR, 1.94	=
Murussi *et al.* (2007)[169]	N	158	41	117	8	6.9	7.3	6.8	eGFR	~103	93	107					↓
Viswanathan *et al.* (2012)[170]	N	152	67	85	11#	~9.9	10.4	9.5	eGFR	~101	93	108					↓
Ruggenenti *et al.* (2012)[62]	N/MA	600	62	538	4#	6.2			Iohexol	101			120	17	7	HR, 2.26	↑
Yokoyama *et al.* (2011)[171]	Any	1002	77	925	3.8#	~6.7	~6.9	~6.7	eGFR	~79	~77	~79					=

Progression (P) or nonprogression (NP) to microalbuminuria or macroalbuminuria. HF, hyperfiltration; N, normoalbuminuria; ↑, increased albuminuria risk; *, adapted from Magee and colleagues;[66] #, median; OR, odds rate; =, no effect on albuminuria risk; ^{51}Cr-EDTA, ^{51}Cr-labeled ethylenediaminetetra-acetic acid; ~, calculated mean; M, males; F, females; MA, microalbuminuria; R, standardized beta; ^{99m}Tc-DTPA, ^{99m}Tc-labeled diethylenetriaminepenta-acetic acid; ↓, decreased albuminuria risk; HR, hazard ratio.

[a]Retrospective cohort study.

[b]GFR was measured 5 years after cohort entry, which was set as baseline value.

[c]Of the 170 patients in the full cohort 63 were excluded, primarily due to the lack of persistent MA.

[d]HF definition was sex specific.

[e]GFR was estimated using Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration 2009, Cockcroft–Gault, and cystatin C–based formulae. Multiple definitions were used to define HF.

[f]Correlation between baseline GFR and UAE at follow-up.

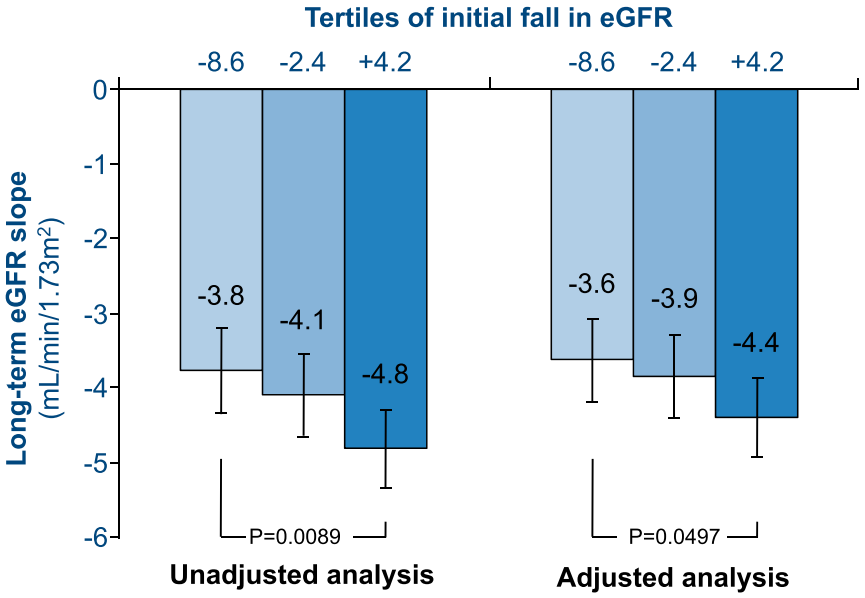


Figure 4. An acute fall in eGFR in losartan-assigned T2DM patients with DKD is inversely correlated with the long-term eGFR slope, after correction for sex, baseline eGFR, diastolic BP, hemoglobin, and urinary albumin-to-creatinine ratio. Data adapted from Holtkamp and colleagues.[75]

suggesting an added renoprotective benefit of these drugs.[73,78,79] Yet, the long-term effect of diet-induced renal hemodynamic alterations (and its amelioration), independent of *e.g.*, an increased renal acid load, on renal outcome in diabetes remains unclear.

CURRENT AND EMERGING TREATMENT OPTIONS

Although glucose-lowering *per se* ameliorates diabetic hyperfiltration, especially in early-onset diabetes,[80] some antihyperglycemic drugs exhibit glucose-independent properties that may directly and/or indirectly benefit this renal risk factor. Here, we briefly discuss a selection of currently available or promising emerging antihyperglycemic (Table 3) and other (nonantihyperglycemic) (Table 4) interventions that may favorably affect renal hemodynamics in human diabetes.

Antihyperglycemic Drugs

SGLT2 Inhibitors

By concomitantly blocking glucose and sodium reabsorption in the proximal tubule, SGLT2 inhibitors not only improve glycemic control by inducing glycosuria in diabetes, but also increase urinary sodium excretion. Their proximal natriuretic effect may be enhanced by accompanied functional blockade of NHE3.[81] Thus, SGLT2 inhibition could reduce (single-nephron) hyperfiltration in diabetes by (*1*) restoring sodium-chloride concentration at the macula densa and subsequent TGF-mediated afferent arteriolar vasoconstriction,[82,83] and (*2*) increasing intraluminal volume causing a retrograde increase in hydraulic pressure in Bowman's space, which constrains filtration pressure.[56] Furthermore, SGLT2 inhibitors consistently reduce bodyweight and BP, and may influence several vascular mediators of renal hemodynamics in both the fasting and postprandial state (*e.g.*, a decrease in atrial natriuretic peptide and insulin, and an increase in glucagon, RAS components, and glucagon-like peptide 1 [GLP–1]).

In an 8-week add-on to insulin study, empagliflozin in uncomplicated T1DM patients with whole-kidney hyperfiltration (mean GFR 172±23 ml/min per 1.73 m^2) demonstrated a glucose-independent 19% decrease in GFR, which was paralleled by a decline in ERPF and estimated P_{GLO} and increase in afferent arteriolar resistance, as assessed by the Gomez equations.[82,83] Finally, as the rise in circulating RAS components may have blunted the renal hemodynamic effect of empagliflozin in these RAS blockade naïve T1DM patients, it is tempting to speculate that combined use of SGLT2 inhibitors and angiotensin converting enzyme inhibitors/ARBs may lead to synergistic renoprotective effects through combined blockade of neurohormonal and tubular factors.[84] Surprisingly, FF increased during euglycemic-clamp conditions in the hyperfiltering patients, underlining the difficulty to unambiguously assess intrarenal hemodynamic changes. In longer-term trials in patients with T2DM, SGLT2 inhibitors initially reduce eGFR over a wide range of baseline values, which appears to be hemodynamically regulated as the reduction reverses after a washout period.[85] In EMPA-REG OUTCOME, 48 months of empagliflozin versus placebo treatment in 7020 high-risk patients with T2DM induced an eGFR trajectory reminiscent of RAS blockade (Figure 5), and resulted in a 46% reduction in the composite of serum creatinine doubling (accompanied by eGFR of ≤45 ml/min per 1.73 m^2), ESRD, or renal death.[86] Notably, over the 34 days after empagliflozin discontinuation, a weekly increase in eGFR of approximately 0.5 ml/min per 1.73 m^2 was observed, as compared with a small decrease in the placebo group. Other long-term SGLT2 inhibition studies in T2DM patients with primary or secondary renal outcomes are underway.[76] Finally, the gastrointestinal effects of novel dual SGLT2/SGLT1 inhibitors (*e.g.*, reduced gastric emptying rate and intestinal glucose uptake) could theoretically also contribute to P_{GLO} reduction after meal ingestion.

GLP-1–Based Therapies

GLP-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase (DPP)–4 inhibitors are associated with renal hemodynamic effects, potentially beyond glycemic control. As such, native GLP-1 infusion

Table 3. Current and emerging antihyperglycemic treatment options with the potential to reduce hyperfiltration in diabetes

Treatment	FDA-Approved Compounds	Route of Administration	Mode of Action	(Potential) Adverse Events[a]	Potential Hyperfiltration-Reducing Mechanism[b]
SGLT2 inhibitor	Canagliflozin Dapagliflozin Empagliflozin	Oral	↑ Urinary glucose excretion	Genital mycotic infections, urinary tract infections, ketoacidosis[c], breast/bladder cancer[c], bone fractures[c], lower limb amputations[c]	Weight loss, BP ↓ TGF activation, P_{BOW} ↑
Dual SGLT1/SGLT2 inhibitor	Phase-3 development	Oral	↑ Urinary glucose excretion ↓ GI glucose uptake	Largely uncertain. Genital mycotic infections, urinary tract infections, GI side effects (nausea, diarrhea), ketoacidosis[c]	Weight loss, BP ↓ GI absorption rate ↓ ANP ↓, GLP-1 ↑ TGF activation, P_{BOW} ↑
GLP-1 receptor agonist	Albiglutide (QW) Dulaglutide (QW) Exenatide (QW, BID) Liraglutide (QD) Lixisenatide (QD) Semaglutide (QD)	Injectable	↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent) ↓ Gastric emptying[d] ↑ Satiety	GI side effects (nausea, vomiting, diarrhea), acute gallstone disease, pancreatitis[c], pancreatic cancer[c]	Weight loss, BP ↓ Gastric emptying rate ↓[d] Glucagon ↓, RAS ↓[172] TGF activation, P_{BOW} ↑
DPP-4 inhibitor	Alogliptin Linagliptin Saxagliptin Sitagliptin	Oral	↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent)	Nasopharyngitis, heart failure[c], pancreatitis[c], pancreatic cancer[c]	Weight loss, BP ↓ Ultrafiltration coefficient ↓[173] Glucagon ↓, RAS ↓[172] TGF activation, P_{BOW} ↑
Thiazolidinedione	Pioglitazone Rosiglitazone	Oral	↑ Insulin sensitivity ↓ Hepatic glucose production	Edema and heart failure, weight gain, bone fractures, bladder cancer[c], CV events[c]	NO-bioavailability efferent arteriole ↑ TGF signaling ↑
Insulin	Insulin lispro	Injectable	↑ Glucose disposal ↓ Hepatic glucose production	Hypoglycemia, weight gain	Postprandial IGF-1–dependent renal vasodilation ↓
Glucagon receptor antagonist	Phase-2 development	Oral/injectable	↓ Glucagon action	Uncertain	TGF activation

FDA, Food and Drug Administration; ↑, increase; P_{BOW}, hydraulic pressure in Bowman's space; ↓, decrease; GI, gastro-intestinal; ANP, atrial natriuretic peptide; QW, once weekly; BID, twice daily; QD, once daily; CV, cardiovascular; NO, nitric oxide; IGF, insulin-like growth factor.

[a]The list of adverse events does not aim to be exhaustive.

[b]Potential mechanisms beyond glucose reduction are listed.

[c]Uncertain safety issues.

[d]Effect on gastric emptying is only sustained with short-action GLP-1 receptor agonists.

Table 4. Current and emerging nonantihyperglycemic treatment options with hyperfiltration-reducing potential in diabetes

Treatment	Intervention/Primary Indication	(Potential) Adverse Events[a]	Potential Hyperfiltration-Reducing Mechanism
Nonpharmacologic interventions			
Nutritional "therapy"	↓ (High)-protein intake	Decreased muscle mass, physical weakness, compromised immune response, decreased bone mineral density	TGF activation, P_{BOW} ↑
	↓ Salt restriction in diabetes	Reduced antihypertensive efficacy	TGF activation, P_{BOW} ↑
Continuous positive airway pressure	↓ Obstructive sleep apnea	Irritation at mask contact points, dryness/irritation of nasal and pharyngeal membranes, eye irritation, nasal congestion and rhinorrhea, claustrophobia, headache, gastric and bowel distention, pneumothorax, recurrent ear and sinus infections	SNS-induced efferent arteriolar resistance ↓[174] ANP ↓[174]
Bariatric surgery	↓ Body weight	Peri- and postoperative complications, reoperation, GI side effects (nausea, vomiting, diarrhea, dumping syndrome), hypoglycemia, nutritional deficiencies, gallstone disease	(Pre-)diabetes ↓, BP ↓ Ultrafiltration coefficient ↓, renal plasma flow ↓ GLP-1 ↑[175] TGF activation
Renal sympathetic denervation	↓ BP	Procedure-related events (renal artery dissection and stenosis, brachycardia, and vascular access complications), postprocedural hypotension	Glomerular size ↓[176] Norepinephrine-induced efferent vasoconstriction ↓[176] Dopamine-induced vasodilation ↓[176]
Pharmacologic			
Carbonic anhydrase inhibitor	↓ Na^+/Cl^- and bicarbonate reabsorption in proximal tubule	Metabolic acidosis, polyuria, paresthesia, tinnitus, dysgeusia, loss of appetite, GI side effects (nausea, vomiting, diarrhea)	TGF activation, P_{BOW} ↑
Mineralocorticoid receptor antagonist	↑ Natriuresis (potassium-sparing)	Hyperkalemia, renal dysfunction, leg cramps, GI side effects (bleeding/ulceration, nausea, vomiting, gastritis, diarrhea), leukopenia/thrombocytopenia	TGF sensitivity ↑
	↓ BP	Spironolactone: gynecomastia, erectile dysfunction, menstrual irregularities	
Endothelin A receptor antagonist	↓ Albuminuria	Fluid retention–related events (peripheral, pulmonary, and facial edema; anemia), congestive heart failure, weight increase	Net efferent arteriolar resistance ↓
COX-2 inhibitor	↓ Inflammation ↓ Pain	CV events, peripheral edema, hypertension, renal injury, GI side effects (bleeding/ulceration, dyspepsia, abdominal pain, diarrhea), upper respiratory tract infections	COX-2 prostanoids ↓[177] RAS ↓[177] Thromboxane A2 ↓[178]
PKC-β inhibitor	Diabetic retinopathy	Dyspepsia, first-degree atrioventricular block, superficial thrombosis, increased blood creatinine phosphokinase, micturition urgency, skin discoloration	Angiotensin II–induced vasoconstriction ↓[179,180]
C-peptide	Improved functional and structural organ-system abnormalities in diabetes[181]	Experimental phase	Afferent arteriolar resistance ↑[182] Efferent arteriolar resistance ↓[182]

↓, decrease; P_{bow}, hydraulic pressure in Bowman's; ↑, increase; SNS, sympathetic nervous system; ANP, atrial natriuretic peptide; Na^+/Cl^-, sodium chloride; GI, gastrointestinal; COX, cyclooxygenase; CV, cardiovascular; PKC, protein kinase C.

[a]The list of adverse events does not aim to be exhaustive.

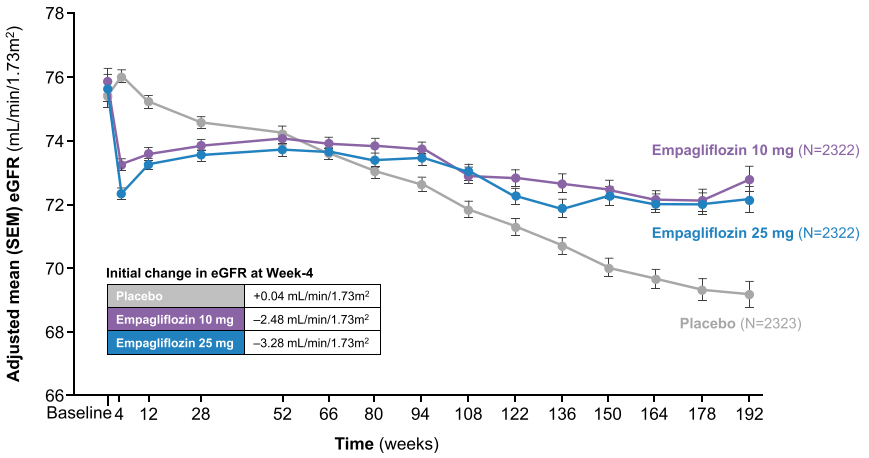


Figure 5. Renal function trajectory in the EMPA-REG OUTCOME trial. In this study, 7020 patients with T2DM at high cardiovascular risk were randomly assigned to receive the SGLT2 inhibitor empagliflozin (10 or 25 mg once daily) or placebo. After an initial drop in eGFR documented at week 4, renal function stabilized in empagliflozin-treated patients over the ensuing follow-up period, whereas among those patients receiving placebo, a steady decline of 1.67 ml/min per 1.73 m^2 per year in eGFR was observed. After 34 days of cessation of the study drug, the initial decrease in eGFR in all empagliflozin-treated patients was completely reversed with an adjusted mean difference from placebo in the change from baseline eGFR of 4.7 ml/min per 1.73 m^2 (not depicted). Adapted from Wanner and colleagues.[86]

reduced creatinine clearance–measured GFR in obese, insulin resistant, hyperfiltering males, 25% of whom were diagnosed with T2DM.[87] The long-acting GLP-1RA liraglutide reversibly reduced measured GFR and UAE in an uncontrolled open-label study involving 31 patients with T2DM.[88] These observations have been attributed to a GLP-1–mediated inhibition of NHE3 (which assembles with DPP-4 in the proximal tubular brush border), thereby reducing proximal sodium reabsorption and GFR through activation of TGF.[51] However, acute administration of GLP-1RA left GFR unaffected in patients with T2DM with normal renal function.[89,90] Moreover, treatment with liraglutide or the DPP-4 inhibitor sitagliptin compared with placebo in normoalbuminuric patients with T2DM (mean GFR 83 ml/min per 1.73 m^2 and FF 23.7%) did not affect eGFR after 2 weeks, nor were there changes in inulin and para-aminohippuric acid–measured renal hemodynamics after 12 weeks.[91] However, although 12-weeks' liraglutide treatment nonsignificantly reduced mean GFR of 75 by 5 ml/min per 1.73 m^2 in 27 albuminuric patients with T2DM with albuminuria, in a placebo-controlled crossover study, GFR decreased by >30% in the two patients with whole-kidney hyperfiltration.[92] Of future interest are postprandial renal hemodynamic actions of short-acting GLP-1RA (which have sustained inhibitory effects on gastric emptying rate and glucagon levels) or DPP-4 inhibitors.

Thiazolidinediones

Twelve-weeks' treatment with the thiazolidinedione rosiglitazone in patients with T2DM with and without albuminuria reduced GFR and FF.[93] These observations were explained by vasodilator actions at the efferent arteriole through increased nitric oxide bioavailability.[93,94] Studies in diabetic rats suggest that restoration of TGF signaling may also play a role.[95]

Insulin

In the fasting state, insulin has been reported to either increase GFR and ERPF, or to have neutral effects, which seems to be dependent on insulin sensitivity.[96,97] Interestingly, in T2DM with macroalbuminuria, the fast-acting insulin lispro blunted postprandial increase in GFR and RPF versus regular insulin, possibly due to inhibition of insulin-like growth factor-1–dependent renal vasodilation.[98]

Glucagon Receptor Antagonists

Hyperglucagonemia in the fasting and postprandial state contributes to elevated blood glucose and hyperfiltration in diabetes.[48,99] Interestingly, glucagon levels increase in the course of DKD.[100] Selective blockade of the glucagon receptor as a novel glucose-lowering target in diabetes could favorably influence renal hemodynamics.[48]

Nonantihyperglycemic Interventions

Nutritional "Therapy"

Improving the diet in diabetes may ameliorate DKD risk, but defining an optimal regime is heavily debated. Importantly, examining its independent influence on (postprandial) hyperfiltration and subsequent renal outcome is virtually impossible, as confounding factors are legion. Nevertheless, extremes of macronutrient intake, especially that of protein, should generally be avoided to reduce hyperfiltration and renal risk.[101] As such, in (pre)hypertensive patients of the OmniHeart study, a high-protein diet (+10% of energy from protein) increased fasting eGFR by approximately 4 ml/min per 1.73 m^2 compared with diets replacing protein with either carbohydrate or fat.[102] Furthermore, guidelines direct to reduce sodium intake to <2000 mg/d in order to prevent renal disease in diabetes.[76] However, clinicians may be reluctant to advocate sodium restriction in diabetes. This is fueled on the one hand by the hypothesis of a "salt-paradox" in diabetes (*i.e.*, a rise in single nephron GFR in response to salt restriction, due to enhanced sensitivity of proximal tubular sodium reabsorption and subsequent inhibition of TGF),[103] and on the other by concerns about sympathetic nervous system and RAS activation with a low-salt diet.[104]

Weight Loss

Although overweight and obesity are independently associated with increases in GFR, ERPF, and FF,[38,105] hyperfiltration is absent in obese nondiabetic patients

when GFR and RPF are indexed for individuals' body surface area (BSA) in many,[11] but not all, studies.[105] The rationale for BSA adjustments comes from observations in mammals that GFR and ERPF are proportional to kidney size, which in turn is typically proportional to body size. Also, dependency of kidney and body size is assumed, as the main function of the kidneys is to regulate total body volume and waste.[106] However, BSA normalizations may not be appropriate given that individuals are endowed with a set number of nephrons, which do not change with weight gain.[106] In addition, formulas like the Du Bois and Du Bois may not be accurate in severely obese (T2DM) subjects.[106] Gastroplasty-induced weight loss from 145 to 97 kg reduced (nonindexed) GFR, ERPF, FF, and albuminuria in nondiabetic subjects.[39] Notably, bariatric surgery in severely obese subjects, of whom 38% had diabetes, has recently been shown to reduce the 4.4-year risk for an eGFR decline of ≥30% and doubling of serum creatinine or ESRD by 58% and 57%, respectively, compared with a matched nonoperated cohort.[77]

Diuretics

The carbonic anhydrase inhibitor acetazolamide decreases sodium, chloride, and bicarbonate reabsorption at the level of the proximal tubule. Although acetazolamide is rarely used as a diuretic because its long-term natriuretic effect is modest,[107] several studies have shown that this drug markedly reduces GFR in T1DM with whole-kidney hyperfiltration[108,109] and DKD,[110] likely by TGF activation and independent from sodium balance.[107] Loop diuretics may not affect TGF, because inhibition of the Na-K-2Cl–cotransporter also blocks solute transport into macula densa cells,[107] although discussion is ongoing.[111] Thiazide diuretics and epithelial sodium channel blockers act distally of the macula densa and do not influence TGF signals. However, (novel selective nonsteroidal) mineralocorticoid receptor antagonists (*e.g.*, spironolactone, eplerenone, finerenone) do induce an initial acute fall in eGFR in T2DM,[112–114] possibly by increasing TGF sensitivity,[115] which predicts a later favorable influence on the course of renal function.[114]

Endothelin-A Receptor Antagonists

Increased endothelin-1 concentrations contribute to DKD development by increasing P_{GLO}, podocyte damage, and permeability to albumin. Conversely, selective endothelin-A receptor antagonists (*e.g.*, avosentan and atrasentan), which alleviate vasoconstriction of the efferent renal arteriole, were shown to increase renal blood flow and reduce renal vascular resistance and FF in hypertensive CKD patients.[116] In line with these hemodynamic observations, long-term treatment with endothelin-A receptor antagonists reduced residual albuminuria by 35%–50% and seemingly preserved renal function in patients with T2DM that were optimally treated for their DKD.[117,118] As the antiproteinuric effect of this drug class is already evident after 1 week of treatment, and in concert with eGFR returns to pretreatment levels after cessation of therapy, a hemodynamic nature of response is suggested.[117,119]

CONCLUDING REMARKS

CKD due to diabetes continues to rise, indicating that current strategies in managing DKD do not suffice to halt renal risk in this population. Accumulating evidence suggests a prognostic and pathogenic role of glomerular hyperfiltration in the initiation and progression of DKD. However, especially as hyperfiltration and albuminuria are renal hemodynamically linked,[76] dedicated prospective studies are needed to confirm whether targeting hyperfiltration improves clinically relevant end points (*i.e.*, 30% or 40% eGFR decline,[120] ESRD, and/or renal death).[76] Several antihyperglycemic and nonhyperglycemic interventions are associated with ameliorated hyperfiltration. Whether these treatments add benefit in the ongoing search for renal risk reduction in diabetes is worth investigating in specifically designed (renoprotection) trials using active comparators, especially in patients with hyperfiltration at baseline.

DISCLOSURES

H.J.L.H. has consulted for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, and ZS-Pharma (all honoraria paid to employer).

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