The impact of hyperfiltration on the diabetic kidney

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Abstract

More than two decades ago, hyperfiltration (HF) in diabetes was postulated to be a maladaptive response observed early in the course of diabetic kidney disease (DKD), which may eventually predispose to irreversible damage to nephrons and development of progressive renal disease. Despite this, the potential mechanisms leading to renal HF in diabetes are not fully understood, although several hypotheses have been proposed, including alterations in glomerular haemodynamic function and tubulo-glomerular feedback. Furthermore, the role of HF as a causative factor in renal disease progression is still unclear and warrants further prospective longitudinal studies. Although HF has been entrenched as the first stage in the classic albuminuric pathway to end-stage renal disease in DKD, and HF has been shown to predict the progression of albuminuria in many, but not all studies, the concept that HF predisposes to the development of chronic kidney disease (CKD) stage 3, that is, glomerular filtration rate (GFR) decline to <60 mL/min/1.73m², remains to be proved. Further long-term studies of GFR gradients therefore are required to establish whether HF ultimately leads to decreased kidney function, after adjustment for glycaemic control and other confounders. Whether reversal of HF with therapeutic agents is protective against reducing the risk of development of albuminuria and renal impairment is also worth investigating in prospective randomized trials.

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1. Introduction

Glomerular hyperfiltration (HF) is a well-characterized phenomenon particularly in Type 1 diabetes (T1DM) that could be described as the earliest stage of classic diabetic kidney disease (DKD) that is referred to as diabetic nephropathy (DN). This phase is followed by the development of microalbuminuria, which heralds the onset of clinical nephropathy [1]. The glomerular filtration rate (GFR) starts to decline with increasing rates of albuminuria and when the macroalbuminuric stage is reached, the GFR declines rapidly, and hypertension develops, eventually manifesting as renal failure.

There is no universally accepted definition for HF, but it is generally defined as a GFR of > 125-140 mL/min/1.73m², which is more than two standard deviations above the mean GFR in healthy controls. This cut-off is dependent upon the GFR methodology used and the study population. HF can also be variably defined as increased filtration fraction, increased filtration per nephron or loss of functional reserve and hence, inability to increase GFR further in response to a high-protein load [2].

While over the past four decades, a number of cross-sectional and longitudinal studies have studied HF in populations with diabetes, the causative or predictive role of HF in the pathogenesis of incipient (microalbuminuria) or overt nephropathy remains largely uncertain [3].

2. Determining GFR in the HF range

HF is difficult to recognize in routine clinical practice because serum creatinine values often remain within normal
laboratory ranges. Various creatinine-based GFR estimates also have inherent limitations when estimating GFR values in the HF range. For instance, the Cockroft-Gault equation overestimates GFR’s in the upper range while the Modification of Diet in Renal Disease (MDRD) formula and even the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula often underestimate high GFR values, especially for patients with diabetes [4–6]. Therefore direct measurements of GFR using clearance techniques with inulin, iohecol, isotoxically labelled iothalamate, ethylene-diamine-tetracetic acid or dithiopentaacetic acid, as a single injection technique or as a steady state infusion, are required to accurately estimate GFR values in the HF range. These methods are cumbersome and not practical for routine clinical use or for large-scale studies. Cystatin C, an endogenous marker that is filtered by the kidneys, has recently been proposed as a more accurate marker of GFR compared to creatinine, particularly in high GFR ranges [7–9].

3. Prevalence of HF

HF is observed in 10%–40% of patients with early T1DM, although prevalence rates of >75% have been reported in some studies (Table 1). In subjects with type 2 diabetes (T2DM), the incidence of HF varies from 0%–40% (Table 2). The wide variation in the reported prevalence of HF is attributed to several reasons, including biological variations in the study population, disease duration, GFR methodology and reference range used.

4. Pathophysiological mechanisms of HF

More than two decades ago, HF in diabetes was postulated to be a maladaptive response to glomerular haemodynamic disturbances observed early in the course of the disease, which may eventually lead to irreversible damage to nephrons and development of DN [29,30]. At a glomerular level, it is caused by increases in the glomerular capillary plasma flow rate and mean glomerular capillary hydraulic pressure. This in turn is due to changes in efferent and afferent arteriolar resistance and changes in systemic arterial pressure [30]. The oncotic pressure gradient across the glomerular capillary filtration membrane and the permeability of the membrane also play a role in determining the filtration fraction. The hypothesis is that HF in diabetes results in irreversible damage to some glomeruli, which diverts the blood flow to the remaining functioning nephrons, resulting in even higher filtration rates in these remaining glomeruli which subsequently causes further nephron loss and ultimately renal failure. A combination of hemodynamic, vasoactive, tubular, growth promoting and metabolic factors most likely contributes to the pathogenesis of HF. The proposed factors affecting glomerular HF in diabetes are summarised in Fig. 1.

4.1. Haemodynamic and vasoactive factors

Increased intraglomerular pressure as a result of increased plasma flow and/or vasodilatation of the afferent glomerular arterioles and/or constriction of the efferent arterioles is a hallmark of early DN. The vasoactive factors that have been implicated in the regulation of glomerular arteriole tone include the renin-angiotensin (R-A) system, the nitric oxide (NO) system and cyclo-oxygenase 2 (COX-2) derived prostanooids.

Enhanced systemic production of R-A has long been recognized as a factor causing exaggeration of intraglomerular pressure and hence HF through relatively greater efferent versus afferent arteriole vasoconstriction [31]. In contrast, in a euglycaemic clamp study involving 36 hyperfiltering T1DM subjects and 40 normofiltering T1DM subjects, HF was associated with an exaggerated suppression of systemic aldosterone levels [32]. This finding is consistent with previous studies which support the existence of a phenomenon known as the “paradox of the low-renin state in diabetes” in humans and rat models of DN [33]. Pharmacological agents blocking the action of the R-A system have been shown to reduce glomerular HF in T1DM [31]. Hence, the mechanisms behind the dissociation between systemic and intra-renal R-A system activity warrant further investigation.

Recently, angiotensin-converting enzyme 2 (ACE2) had been implicated in the induction and maintenance of HF in experimental diabetes. ACE2 is a key enzyme involved in the degradation of angiotensin II and hence, the formation of angiotensin 1–7, a known vasodilator of the glomerular afferent arteriole. ACE2 knockout mice and mice in which ACE2 activity has chronically inhibited have been shown to lack the ability to develop HF or increase glomerular hydrostatic capillary pressure in response to hyperglycaemia or a high-protein diet [34].

Non-peptide vasoactive agents may also be involved in the mediation of vascular changes seen in early nephropathy. For instance, hyperglycaemia induced increased NO synthesis has been associated with HF [35–37]. However, it is not clear if the changes in NO production play a causal role in the pathogenesis of glomerular HF or whether it is merely a bystander secondary to increased renal blood flow. COX-2 derived prostanooids have also been shown to modulate afferent arteriolar function, leading to HF. Further evidence that implicates COX-2 as a modulator of HF includes the fact that it is expressed in endothelial cells in renal tissue and mediates renal auto-regulatory effects at the macula densa [38].

4.2. Tubular factors

Major systemic factors that have been incriminated as causes of HF in diabetes are acute or chronic hyperglycaemia and excess tubular sodium (Na), by means of suppression of tubuloglomerular feedback via their effects on the macula densa. Evidence exists in diabetic rats and humans for a primary increase in proximal tubular Na and glucose reabsorption, due to augmented Na-glucose co-transport, that results in a reduced sodium chloride (NaCl) concentration being delivered to the macula densa. This reduction in NaCl concentration is interpreted by the juxtaglomerular apparatus to represent a decline in circulating volume and renal perfusion. Therefore, to maintain GFR, dilatation of the afferent glomerular arterioles occurs, possible through an adenosine-mediated process, which ultimately results in a state of HF [30,39].

High dietary Na intake has also been proposed as an alternative tubular mechanism of HF as a result of dysfunction of the
HF: hyperfiltration; T1DM: type 1 diabetes mellitus; GFR: glomerular filtration rate; NA: normoalbuminuria; MA: microalbuminuria; P: proteinuria; EDTA: ethylene-diamine tetraacetic acid; Na: sodium; ACR: albumin to creatinine ratio; LDL: low density lipoprotein; CKD-EPI: chronic kidney disease-epidemiology formula.

Table 1
Summary of prevalence studies of HF in T1DM.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>HF threshold (mL/min/1.73m²)</th>
<th>GFR method</th>
<th>Prevalence of HF</th>
<th>Correlations with HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotroneo et al., [10] (1998)</td>
<td>n = 177 Normotensive/NA</td>
<td>&gt; 135</td>
<td>IV bolus</td>
<td>55.9% (99/177)</td>
<td>Age/sex/metabolic control</td>
</tr>
<tr>
<td>Dahlquist [11] (2001)</td>
<td>n = 75 NA/MA</td>
<td>&gt; 125</td>
<td>EDTA/hippuran injection</td>
<td>40% (30/75)</td>
<td>Higher baseline GFR was a risk factor for MA or P</td>
</tr>
<tr>
<td>Amin et al., [12] (2005)</td>
<td>n = 308 NA</td>
<td>&gt; 125</td>
<td>Single inulin injection</td>
<td>67.8% (205/308)</td>
<td>Puberty/increased ACR/poor glycaemic control</td>
</tr>
<tr>
<td>Vervoort et al., [13] (2005)</td>
<td>n = 54 NA</td>
<td>&gt; 130</td>
<td>IV bolus</td>
<td>25% (13/54)</td>
<td>Proximal tubular Na absorption</td>
</tr>
<tr>
<td>Thomas et al., [16] (2012)</td>
<td>n = 2318 NA</td>
<td>&gt; 125</td>
<td>CKD-EPI formula</td>
<td>10% (232/2318)</td>
<td>Male/younger/smaller stature/current smokers</td>
</tr>
<tr>
<td>Bulum et al., [17] (2013)</td>
<td>n = 313 NA</td>
<td>&gt; 125</td>
<td>CKD-EPI formula</td>
<td>12% (38/313)</td>
<td>Younger/shorter disease duration/lower total and LDL-cholesterol/Higher HbA1c</td>
</tr>
</tbody>
</table>

HF: hyperfiltration; T1DM: type 1 diabetes mellitus; GFR: glomerular filtration rate; NA: normoalbuminuria; MA: microalbuminuria; P: proteinuria; EDTA: ethylene-diamine tetraacetic acid; Na: sodium; ACR: albumin to creatinine ratio; LDL: low density lipoprotein; CKD-EPI: chronic kidney disease-epidemiology formula.

tubulo-glomerular feedback mechanism caused by increasing proximal tubular Na resorption [13,40]. HF in this setting may be an appropriate compensatory mechanism from a renal viewpoint since it counteracts the effect of enhanced Na proximal tubule reabsorption, thereby returning distal sodium and water delivery towards normal and preventing excess fluid retention.

Recently, during clamped euglycaemia, HF patients with T1DM (inulin GFR ≥ 135 mL/min/1.73m²) have been shown to have a lower fractional excretion rate of Na compared with normofiltering T1DM or health controls. The authors of this study attributed the lower fractional excretion rate of sodium in HF patients to increased sodium-glucose transport in the proximal renal tubules. Interestingly, under clamped hyperglycaemic conditions, a further decrease in the fractional excretion rate of Na was not seen. A decrease in the fractional excretion rate of Na could have been expected due to the further delivery of glucose to the proximal tubule and hence exaggerated sodium-glucose co-transport in the proximal tubule. Indeed, the fractional excretion rate of sodium was increased in HF T1DM patients during hyperglycaemic condition with increases in GFR being positively correlated with increases in the fractional excretion rate of Na. This finding suggests that the mechanisms responsible for increased Na reabsorption leading to HF can be saturated and that other factors such as activation of vasoactive substances are important in promoting HF in the setting of hyperglycaemia [41].

4.3. Metabolic and other factors

It is also worth noting that the mechanisms linking tubulo-glomerular feedback to HF are still not fully defined. Diabetes-induced HF has been shown to occur in adenosine A1-receptor deficient mice, which lack the tubulo-glomerular feedback mechanism [42]. Reduced proximal intra-tubular pressure as a result of increased proximal tubular electrolyte reabsorption has also been implicated in the development of HF, independent of tubulo-glomerular feedback mechanisms. Reductions in intra-tubular pressure have been linked to reduced pressures in Bowman’s space which in turn increase the pressure gradient over the filtration barrier contributing to the development of HF [43].

Table 2

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>HF threshold (mL/min/1.73m²)</th>
<th>GFR method</th>
<th>Prevalence of HF</th>
<th>Correlations with HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebovitz and Palmisano</td>
<td>n = 20</td>
<td>140</td>
<td>Iothalamate constant infusion</td>
<td>35% (7/20)</td>
<td>Shorter disease duration</td>
</tr>
<tr>
<td>Vora et al., [19]</td>
<td>n = 110</td>
<td>140</td>
<td>Single shot EDTA by bi-exponential analysis</td>
<td>16% (18/110)</td>
<td>Effective renal plasma flow, younger age</td>
</tr>
<tr>
<td>(1992)</td>
<td>Normotensive Caucasian patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gragnoli et al., [20]</td>
<td>n = 163</td>
<td>139</td>
<td>DTPA scintigraphy using Gates method</td>
<td>6% (10/163)</td>
<td>Negative correlation with blood pressure</td>
</tr>
<tr>
<td>(1993)</td>
<td>Italian NA and MA subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silveiro et al., [21]</td>
<td>n = 71</td>
<td>137</td>
<td>EDTA single injection (B-M correction not stated)</td>
<td>21% (15/71)</td>
<td>Fasting BSL, glucosuria, younger age, total cholesterol</td>
</tr>
<tr>
<td>(1993)</td>
<td>Brazilian non-P patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruce et al., [22]</td>
<td>n = 15</td>
<td>140</td>
<td>EDTA</td>
<td>73% (11/15)</td>
<td>BMI and AER</td>
</tr>
<tr>
<td>(1994)</td>
<td>Normotensive, Polynesian subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al., [23]</td>
<td>n = 284</td>
<td>140</td>
<td>EDTA clearance method (B-M corrected)</td>
<td>25% (71/284)</td>
<td>Shorter disease duration, younger age</td>
</tr>
<tr>
<td>Keller et al., [24]</td>
<td>n = 85</td>
<td>131</td>
<td>Inulin steady-state clearance</td>
<td>58% of recent onset &lt; 1 yr</td>
<td>Fasting glucose</td>
</tr>
<tr>
<td>(1996)</td>
<td>Caucasian subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vdel et al., [25]</td>
<td>n = 158</td>
<td>140</td>
<td>Single iv bolus of EDTA (B-M corrected)</td>
<td>23% for MA patients (37/158)</td>
<td>Younger age, shorter disease duration, higher HbA1c, urinary Na excretion</td>
</tr>
<tr>
<td>(1996)</td>
<td>NA n = 39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chaiken et al., [26]</td>
<td>n = 194</td>
<td>140</td>
<td>123I-iotalamate constant infusion</td>
<td>17% (34/194)</td>
<td>Younger age</td>
</tr>
<tr>
<td>Guizar et al., [27]</td>
<td>n = 28</td>
<td>GFR’s pre- and post-protein load</td>
<td>DTPA</td>
<td>72% (20/28)</td>
<td></td>
</tr>
<tr>
<td>(2001)</td>
<td>Mexican subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruggenenti et al., [28]</td>
<td>n = 600</td>
<td>120</td>
<td>Iohexol</td>
<td>15% (90/600)</td>
<td>Younger, higher HbA1c, TG</td>
</tr>
<tr>
<td>(2012)</td>
<td>Caucasian, NA, hypertensive subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HF: hyperfiltration; T2DM: type 2 diabetes mellitus; GFR: glomerular filtration rate; NA: normoalbuminuria; MA: microalbuminuria; P: proteinuria; B-M: Brochner-Mortensen; EDTA: ethylene-diamine tetraacetic acid; DTPA: diethylene triamine pentaacetic acid; Na: sodium; BMI: Body Mass Index; AER: albumin excretion rate; BSL: blood sugar level; TG: triglycerides

It is also worth noting that the mechanisms linking tubulo-glomerular feedback to HF are still not fully defined. Diabetes-induced HF has been shown to occur in adenosine A1-receptor deficient mice, which lack the tubulo-glomerular feedback mechanism [42]. Reduced proximal intra-tubular pressure as a result of increased proximal tubular electrolyte reabsorption has also been implicated in the development of HF, independent of tubulo-glomerular feedback mechanisms. Reductions in intra-tubular pressure have been linked to reduced pressures in Bowman’s space which in turn increase the pressure gradient over the filtration barrier contributing to the development of HF [43].

4.3. Metabolic and other factors

As suggested above, the production and bioavailability of vasoactive mediators are further enhanced in the presence of hyperglycaemia [44]. A recent study of 32 T1DM subjects demonstrated the effects of acute hyperglycaemia [45]. Hyperglycaemia increased the mean GFR by 15% and 17% when measured by Cystatin C and inulin clearance, respectively [45]. In contrast, resolution of HF by re-establishing a normoglycaemic state has been proven in multiple studies in the past [46,47].

Other mechanisms postulated in the development of DN involve the activation of protein kinase C and increased levels of reactive oxygen species and advanced glycation end products (AGEs) [48]. However, why these intraglomerular mechanisms are preferentially activated in some individuals and not others is poorly understood and may be related to genetic factors. These functional changes lead to the typical structural abnormalities seen in early diabetes, including increased glomerular capillary area, basement membrane thickening and mesangial proliferation [49,50].

Circulating biomarkers of oxidative stress have been reported to be elevated in young HF T1DM patients compared with age matched control subjects [51]. Furthermore, in a multivariate analysis higher levels of markers of oxidative stress were significantly associated with higher levels of creatinine clearance together with HbA1c and albuminuria. Recently, HF patients
with T1DM have been shown to have increased urinary excretion of inflammatory cytokines/chemokines compared with normofiltering patients with T1DM. This finding is consistent with the concept that the high intraglomerular pressure associated with HF results in increased shear stress leading to renal injury [52].

HF is also associated with a number of clinical conditions other than diabetes, such as systemic hypertension, impaired nocturnal blood pressure dipping, obesity/metabolic syndrome and abnormalities in systemic vascular function including endothelial dysfunction [37,39,53,54].

5. HF at whole-kidney and single-nephron level

HF at a glomerular level can occur with congenital or acquired reduction in renal mass. Most long-term studies of non-diabetic subjects with single kidneys arrive at the conclusion that HF in the remaining kidney per se following uni-nephrectomy does not lead to renal impairment. The difference in the pathogenic role of HF in diabetes and non-diabetic single-kidney could be related to the different origins of HF in the two settings. In single-kidney subjects, HF is shown to be secondary to increased renal plasma flow whereas in diabetes, this is attributed to a multitude of factors as discussed previously.

HF is arbitrarily defined as being present when whole-kidney GFR exceeds 125 to 140 mL/min/1.73m² in an individual with two functioning kidneys. In early diabetes, HF at the whole-kidney level may reflect a generalised increase in single-nephron GFR, but a contribution by increased nephron endowment cannot be ruled out. Soon after the onset of DN, early decreases in whole-kidney GFR may reflect a generalised decrease in single-nephron GFR. By contrast, at later stages of nephropathy, nephron dropout leads to compensatory HF in remaining nephrons [55].

In animal models of renal damage, including DN, a decrease in dietary protein intake retards the progression of renal disease while decreasing HF at single-nephron level [56,57]. Similarly, in patients with T1DM and GFR < 60 mL/min/1.73m², a reduction of dietary protein intake from 1.0–1.1 to 0.6–0.7 g/kg daily has been shown to slow the annual rate of decline of GFR from between 6 and 10 to less than 2 mL/min/1.73m² [58,59]. This is consistent with the concept that HF at single-nephron level may contribute to GFR decline at whole-kidney level in advanced kidney disease. However, a link between HF at the whole-kidney level and subsequent progressive GFR decline to subnormal levels has not yet been established in human diabetes.

6. HF and nephromegaly

Structurally, HF is closely correlated with glomerular hypertrophy and increased filtration surface area [60] and nephromegaly [61] and structural changes including basement membrane thickening and mesangial matrix expansion have been observed in this early phase of disease [50,62,63], but detection requires a kidney biopsy. Previous studies suggest that the cause of such changes may involve hormonal factors acting at the proximal tubule resulting in tubular growth and subsequent increased kidney mass in early diabetes [13,40]. In experimental studies, blocking the enzyme ornithine decarboxylase, the rate-limiting step in renal tubular growth, results in an attenuation of kidney growth and a reduction in GFR [64].

HF and renal enlargement are both associated with early diabetes and distinguishing one from the other is difficult. Early studies in young adults with T1DM and elevated GFR showed that kidney weight, corrected for body surface area, was increased by 22% after a mean duration of diabetes of 4.9 years. However, GFR per gram of kidney weight was the same in diabetic and control participants [65].

It has been suggested that HF is a pathogenetic factor for nephromegaly in humans, but in animal models of diabetes renal enlargement precedes HF [66,67]. Dissociation between the processes of HF and nephromegaly in diabetes has been shown in a knockout Na-glucose transporter (SGLT-2) model of experimental diabetes. Knockout SGLT-2 mice with diabetes had lower blood glucose levels and GFR values compared to wild-type mice with diabetes but renal growth and markers of renal inflammation and fibrosis were not attenuated in the absence of SGLT-2 [68].

A cross-sectional study of 177 adolescents with T1DM showed that renal enlargement is associated with microalbuminuria as well as with puberty duration. Participants with kidney volume > 300 mL/1.73m² were eight times more likely to have microalbuminuria than those with kidney volume < 300 mL/1.73m² [69]. In a longitudinal study of 146 normoalbuminuric patients with mean duration of T1DM of 9.5 years, increased kidney volume at baseline, but not HF, was a predictor of progression to microalbuminuria in 27 patients. Patients predisposed to microalbuminuria showed a stable increase in kidney volume along with a faster initial decline in GFR. However, mean attained GFR remained within the normal range over 4 years, indicating that resolution of HF could not be separated from onset of a progressive decline in GFR to subnormal levels. Also, the possibility that HF prior to the study was related to the development of microalbuminuria could not be excluded [70]. Further work is therefore needed to establish a pathogenetic role for HF and/or nephromegaly in DN.

In summary, hypertrophy of the diabetic kidneys has been linked to the development of microalbuminuria compared to normal sized kidneys, as discussed above, and an increased risk of developing end-stage kidney disease (ESKD) [71]. Kidney hypertrophy most likely represents a maladaptive response to hyperglycaemia and the release of various cytokines and growth factors such as insulin-like growth factor (IGF)-1, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF) and possibly through adenosine monophosphate (AMP)-activated protein kinase, a key player in regulating kidney metabolism that predisposes to the development of DKD [71].

7. Clinical significance of HF

The clinical significance of HF lies in its ability to predict the onset of albuminuria and/or a decline in renal function. In current clinical practice, determination of microalbuminuria is
considered as the earliest and the best predictor of diabetic glomerular involvement. As HF precedes the development of microalbuminuria, this may be an even earlier indicator of or predictor of renal involvement. Moreover, acute or chronic hyperglycaemia may influence GFR and albuminuria levels, and may therefore confound the evaluation of HF as an independent risk factor for development of DN. Many studies have attempted to determine the predictive role of HF for subsequent development of insipient (microalbuminuria) or overt nephropathy, however, the study outcomes so far have been ambivalent.

In a Swedish study, a steep decline in renal function of 11 mL/min/year over about 5 years has been demonstrated in patients with T1DM and HF compared with a rise of 0.8 mL/min/year in normofiltering patients [72]. The rate of decline in GFR was positively correlated with glomerular basement membrane thickness and interstitial volume fraction and mean HbAlc level. The authors concluded that a decreasing GFR in the early microalbuminuria stage may be due to advancing glomerulopathy. In a similar study involving 75 subjects with T1DM (60 of whom completed the study), hyperfiltration (GFR > 125 mL/min/1.73m²) carried a 53% risk of development of microalbuminuria compared with 5% in those with a GFR < 125 mL/min over a 29-year follow-up period [11]. The study concluded that baseline elevated GFR was a weaker predictor for the subsequent development of DN (defined as development of micro- or macroalbuminuria) compared to a baseline elevated albumin excretion rate (AER) > 15 mg/min.

Glomerular HF was associated with puberty and predicted increasing urinary albumin to creatinine (ACR) levels and microalbuminuria, independent of HbA1c in the Oxford regional prospective study, involving 308 children followed up from diagnosis of T1DM for 11 years [12]. A 10-year follow-up study of 146 individuals with T1DM revealed that baseline increased kidney volume rather than high GFR predicted the development of microalbuminuria, along with a faster decline of GFR [70].

A recent meta-analysis of 10 cohort studies totalling 780 subjects with T1DM followed-up for a median of 11 years concluded that glomerular HF increased the risk of albuminuria and progression of DN. The relative risk of progressive albuminuria was 2.71 in those with HF versus normal GFR at baseline. HF was associated with higher HbAlc in this study [15].

However, the concept of HF being a predictor of microalbuminuria or subsequent renal failure in T1DM is not a universal finding. In a case-controlled prospective study of 10-years of follow-up of 50 children with T1DM, the final GFR remained higher in the group with HF vs controls (122 vs 103 mL/min/1.73m²) despite a non-significantly faster decline of GFR in the HF compared with that of the control group. A similar number of each group progressed to either micro- or macroalbuminuria or developed hypertension. However, the end-of-study AER was higher in the HF group and baseline HF was an independent determinant of end-of-study blood pressure. The authors concluded that blood pressure and AER were the main risk factors for renal outcomes, rather than HF [73].

A 15-year follow-up study of 426 T1DM subjects [14] did not show a predictive role of HF in the development of microalbuminuria, and another study from the same centre involving 301 subjects followed-up for 8–12 years, failed to show a causative association between HF and subsequent GFR decline [74]. Similar findings were obtained from a larger Finnish study of 2318 Type 1 diabetic subjects followed up for a median of 5.2 years, which also failed to demonstrate an association between glomerular HF and subsequent renal disease defined in terms of development of micro- or macroalbuminuria [16].

A pooled analysis of 12 observational studies in T1DM also did not show a strong relationship between HF and increases in AER [3] (Fig. 2). Five of the studies included in this analysis categorized participants according to baseline HF or normofiltration and followed up for 3–18 years (Fig. 2A). Although there was a greater decline in GFR in the cohorts eliciting baseline HF, the final mean GFR remained at or above 100 mL/min/1.73m², and therefore inconclusive in terms of establishing HF as a risk factor for renal impairment. In five other studies (Fig. 2B), categorized according to progression or non-progression of AER, the absolute decline of GFR in progressors was at least twice that of non-progressors. There were only 2 studies in this series that linked initial HF to both subsequent increases in AER and decline in GFR, however the study cohorts were very small and the baseline AER was not recorded to compare with the other studies. Therefore, whether an early decline in GFR in HF subjects observed in these studies represents resolution of HF or an early stage of renal impairment cannot be answered by studies that have been performed to date.

The pathogenic role of glomerular hyperfiltration is even less clear in T2DM, due to paucity of long-term studies, difficulties in determining the exact onset of the diabetes, coexistence of reno-vascular disease and the vast heterogeneity of patient characteristics. In longitudinal studies in T2DM, HF has been associated with a greater rate of decline in GFR compared to normofiltering subjects and non-diabetic controls over a 6-year period [75]. However, this has not been a universal finding [26]. A recent study of 600 hypertensive T2DM patients with normo- or microalbuminuria, 90 with HF at baseline, showed a faster decline in renal function and progression of albuminuric status over a mean follow-up period of 4 years in patients with persistent HF versus those with normal GFR at baseline and those who had their HF at baseline ameliorated at six months by intensive BP and metabolic control. Eleven of 47 (23.4%) patients with persistent HF progressed to micro- or macroalbuminuria versus 53 (10.6%) of the 502 who had their HF ameliorated at 6 months or were nonhyperfiltering since inclusion [28].

The challenge in carrying out studies to establish a relationship between the state of HF and an increased risk for a rapid decline in GFR and achieving a GFR < 60 mL/min/1.73m² is the long duration between early HF and the development overt DN, which could span 2–3 decades. Resolution of HF may be largely a functional and potentially beneficial process as opposed to the detrimental process of nephron loss that eventually leads to irreversible loss of renal function. Differentiation of these two processes has been a challenge, as there are no studies reported that follow-up patients from the early stages of HF to stages of significant renal impairment (i.e. GFR < 60 mL/min/1.73m²). Furthermore, accessibility of serial renal biopsy data, which may be useful in differentiating between these two entities, is limited.
Fig. 2. The two groups (panel A and panel B) show mean baseline and final GFR in subgroups from 12 observational studies of GFR trajectory over 3 to 18 years in type 1 diabetes. Subgroups are distinguished by colour of symbols (black vs white), study duration was in years as indicated. The initial and the final GFR in the subgroups of each study are represented by the same symbol and joined by a solid line to form a dumb-bell symbol. As baseline, GFR exceeded final GFR in all subgroups, the dumb-bells represent the decline in GFR during the study. The six studies in A [12,73,110-113] show prospective GFR data in subgroups categorised according to the presence of hyperfiltration (HF) or normofiltration (NF) at baseline. In five of these studies, GFR decline was compared in subgroups with baseline hyperfiltration or normofiltration, with the corresponding number (n) of participants as listed (parentheses). One study (Amin et al. [12]) shows GFR decline in combined hyperfiltration and normofiltration subgroups. Black circles, hyperfiltration; white circles, normofiltration; black triangles, hyperfiltration and normofiltration. The six studies in B [70,114-118] show GFR data in subgroups categorised, retrospectively according to progression or non-progression of albumin excretion rate (AER) to at least microalbuminuria during the study. In five of these studies, GFR decline was compared in progressors and non-progressors, with the corresponding number (n) of participants as listed (parentheses). One study (Chiarelli et al. [118]) shows GFR decline only in progressors. Black squares, progression of AER; white squares, non-progression of AER. Reproduced and modified from Jerums et al., 2010 [3] with permission, note reference number annotation has been changed from the original figure so that they are specific for this current article.

8. Association of HF with obesity/metabolic syndrome and vascular disease

The association between HF and the obesity-metabolic syndrome in diabetic as well as non-diabetic subjects is...
well-established [39] and the prevalence of overweight/obese subjects among T1DM and T2DM cohorts can be as high as 55% and 86%, respectively [78]. Moreover, insulin resistance, obesity and metabolic syndrome are associated with renal disease processes that are similar to those observed in diabetes. The vasoactive mediators postulated in the pathophysiology of DN, such as TGF-β have also been implicated in obesity-induced glomerular injury [79].

Studies based on assessments of GFR and adiposity have documented that the risk of HF is higher in obese subjects compared with the normal controls [80]. Weight excess is associated with an altered renal haemodynamic profile, i.e. an increased glomerular filtration rate relative to effective renal plasma flow, resulting in an increased filtration fraction [81]. Augmented tubulo-glomerular feedback, proximal tubular Na resorption, increased plasma volume secondary to salt retention and systemic hypertension are hallmark features in obese patients, similar to that observed in diabetes [82]. Furthermore, recent evidence showed that a central body fat distribution is also associated with an increased filtration fraction, even independent of overall weight excess [83]. Insulin resistance causes an imbalance between afferent and efferent arterial vasomotor activity, increasing transcapillary pressure gradient causing glomerular HF. Additionally, the role of insulin is mediated through stimulation of synthesis of IGF-1 and IGF-2, both of which promote glomerular hypertrophy [84]. These alterations in the renal haemodynamic profile are associated with adverse renal outcomes in experimental models and in human renal transplant recipients. They are also associated with a decrease in urinary Na excretion, and are reversible by weight loss, R-A-aldosterone system blockade and by dietary Na restriction.

Adipocytokines such as adiponectin, resistin and leptin present in adipose tissue have been implicated in pathological renal manifestations in several studies [85–88]. Elevated leptin levels have been linked to glomerular HF in experimental models of T2DM, and the role of leptin as a potent stimulator of proliferation within cellular compartments of the glomeruli has also been documented [88,89]. Adipocytokine genes including the leptin receptor genes were overexpressed in the glomeruli of patients with obesity-related glomerulopathy when compared to normal controls [90].

The above studies suggest that adipocytokines may be implicated in the observed association between increased adipose tissue mass in obesity and glomerular HF, with the potential to contribute to subsequent development of glomerular disease. Whether this metabolic-related glomerular HF early in life translates to a higher risk of cardiovascular morbidity and mortality in later years, compared to normofiltering counterparts, remains to be confirmed in prospective studies.

HF has been linked with early systemic vascular abnormalities and endothelial dysfunction in various studies. In a cohort of patients with uncomplicated T1DM, HF was associated with high arterial compliance and an impaired vasodilatory response to reactive hyperemia [37,54]. The authors interpreted their observations as reflecting the underlying state of maximum vasodilation and consequent inability to further vasodilate in response to ischaemic stimuli.

HF has been associated with elevations in systolic and diastolic blood pressures as well as disturbances in the diurnal blood pressure patterns in early T1DM, although the long-term clinical significance of these subtle cardiovascular abnormalities is yet to be elucidated. For instance, nocturnal non-dipping blood pressure status has been shown to be related to renal morphological changes and long-term HF in a study of 40 normoalbuminuric adolescents and young adults, despite a short duration T1DM [91]. A relationship of glomerular HF with a blunted nocturnal decrease in diastolic blood pressure has been documented in another study involving 38 normotensive normoalbuminuric T1DM subjects [53]. HF was associated with higher heart rate and systolic blood pressure values and a paradoxical suppression of systemic aldosterone levels, in a group of T1DM patients studied under euglycaemic clamp conditions [32].

Recently, an association has been reported between elevated GFR levels and cardiovascular disease and also total mortality. In a large group of patients with type 1 diabetes that were followed for a median of 7 years, those with an estimated GFR (derived from MDRD formula) > 120 mL/min/1.73m² at baseline had increased mortality rates compared to those with estimated GFR values of 60–120 mL/min/1.73m², independent of the degree of albuminuria [92]. Furthermore, a large meta-analysis has shown that in individuals with and without diabetes who do not have albuminuria, those with estimated GFR > 105 mL/min/1.73m² have a 27% increase in the hazard ratio for all-cause mortality and a non-significant 19% increase in cardiovascular mortality compared to individuals with estimated GFR levels between 90–104 mL/min/1.73m² [93].

In a recent study of non-diabetic individuals who had direct measurement of GFR (iohexol clearance), those in the top quartile of GFR (mean 108 mL/min/1.73m²) had a greater frequency of subclinical cardiovascular disease of the carotid arteries and heart compared to those in the lowest GFR quartile (mean GFR 78 mL/min/1.73m²), independent of albuminuria, blood pressure, body mass index, smoking status and fasting glucose levels [94]. The mechanisms that link HF with cardiovascular disease remain unknown. It has been suggested that HF should be viewed as a risk marker for cardiovascular disease, and that HF is caused by one or more risk factors that are also responsible for the development of cardiovascular disease [95].

9. Reversing glomerular HF

If sufficient evidence for an association between HF and the subsequent development of renal impairment was to be established, there would be a case for intervention studies to assess the effect of normalization of GFR on subsequent development of DN. A summary of interventions that have been performed in an attempt to reverse HF is shown in Table 3.

One of the most important determinants of HF is hyperglycaemia. Early HF, occurring in the first months of T1DM has been shown to reverse with insulin therapy [46]. By contrast, late or persistent HF may persist for years and may not be associated with glycaemic control when assessed by HbA1c measurements several years after the onset of diabetes. In a study involving 12 patients with T1DM and an increased GFR for a year after
they were randomly assigned either to continuous subcutaneous insulin pump therapy or to unchanged conventional therapy, the glomerular filtration rate fell significantly in the pump group and became normal in four of the six patients although the kidneys remained enlarged. GFR did not change in the conventional-treatment group. Therefore, these results support the theory that strict glycaemic control normalizes the GFR, at least in the first years after the development of diabetes. The effects of improving glycaemic control on HF are less well-documented in patients with long standing diabetes [61].

Control of other pathogenetic factors that contribute to glomerular HF in diabetic subjects apart from hyperglycaemia would be beneficial in resolving HF and arresting progressive renal damage. Short-term use of continuous positive airway pressure is shown to ameliorate glomerular HF in patients with obstructive sleep apnoea syndrome [103]. Similarly, the avoidance of obesity, or weight loss will remove a synergistic factor for HF and glomerular injury, thus delaying the progression to end-stage renal disease in diabetic subjects. In eight subjects with severe obesity (body mass index > 48 kg/m²), their mean GFR reduced from a mean of 145 to 110 mL/min following significant weight loss [96].

Renal injury associated with glomerular HF may be mediated by activation of the R-A system, which leads to maladaptive intra-renal and systemic hemodynamic responses, increased arterial stiffness and endothelial dysfunction, as discussed previously. The most effective intervention to obliterate glomerular HF, therefore, may be to target glomerular hypertension by blocking the R-A system. The increase in glomerular pressure could be attenuated by blocking the vaso-constrictive effect of angiotensin II on the glomerular efferent arteriole, and thereby, reduce glomerular HF. Such a beneficial effect would be independent of the systemic antihypertensive properties of agents, which interfere with the R-A system.

Many randomized, controlled trials in humans confirm that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause regression of albuminuria and retard the progression of DN. Evidence also exists for at least partial reversal of HF with the use of ACEIs in T1DM [31]. A recent analysis demonstrated that the initial decrease in GFR caused by angiotensin II inhibition resulted in a better long-term outcome for preservation of kidney function [97]. However, ACEIs, ARBs and even a combination of the two classes are limited in the extent to which they inhibit

<table>
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<th>Intervention</th>
<th>Study subjects</th>
<th>Mechanism</th>
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<tr>
<td>Treatment of hyperglycaemia</td>
<td>T1DM subjects</td>
<td>Removal of suppression of tubulo-glomerular feedback mechanism</td>
<td>Mogensen [46]</td>
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<td>Weight loss</td>
<td>Obese subjects</td>
<td>Reduction of renal plasma flow and filtration fraction</td>
<td>Wiseman et al., [61]</td>
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<tr>
<td>R-A system blockade</td>
<td>T1DM (Sochett) and T2DM subjects</td>
<td>Blockade of vaso-constrictive effect of angiotensin II on the glomerular efferent arteriole</td>
<td>Sochett et al., [31]</td>
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<tr>
<td>Thiazolidinediones</td>
<td>T2DM subjects</td>
<td>Improvement of nitric oxide bioavailability and amelioration of renal glomerular endothelial dysfunction</td>
<td>Holtkamp et al., [97]</td>
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<tr>
<td>SGLT-2 inhibitors</td>
<td>T1DM subjects</td>
<td>Removal of suppression of tubulo-glomerular feedback mechanism</td>
<td>Cherney et al., [99]</td>
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<td>(2013)</td>
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<tr>
<td>COX-2 inhibitors</td>
<td>T1DM subjects</td>
<td>Obliteration of COX 2 prostanoid induced afferent arteriolar dilation</td>
<td>Cherney et al., [44]</td>
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<tr>
<td>C-peptide</td>
<td>Animal model</td>
<td>Dilatation of the efferent arteriole and inhibition of tubular Na reabsorption</td>
<td>Nordquist et al., [100]</td>
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<tr>
<td>PKC-beta inhibitors (Ruboxistaurin)</td>
<td>Animal model</td>
<td>Obliteration of the effects of PKC-β induced intracellular pathways</td>
<td>Koya et al., [101]</td>
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<tr>
<td>Renal sympathetic denervation</td>
<td>Animal model</td>
<td>Removal of renal sympathetic nerve stimulation</td>
<td>Luippold et al., [102]</td>
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<tr>
<td>Continuous positive airway pressure</td>
<td>Obese patients with Obstructive Sleep Apnoea Syndrome</td>
<td>Reduction in sympathetic activity and vasoactive factors</td>
<td>Kinbuchi et al., [103]</td>
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HF: hyperfiltration; R-A: renin-angiotensin; SGLT-2: sodium-glucose co-transporter-2; COX: cyclo-oxygenase; PKC: protein kinase C; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.
the activity of the R-A system and hence offer only partial renal protection. Angiotensin II and aldosterone breakthrough due to activation of compensatory pathways may be important mechanisms that would explain the limited efficacy of ACEIs and ARBs [14,99,104]. By contrast, direct renin inhibition theoretically has physiologic advantages that would result in complete blockade of the R-A system. However, the effectiveness of these agents in abolishing HF is yet to be proven in clinical studies, and is unlikely to ever be undertaken given the adverse clinical outcomes that have been reported for the combination of direct renin inhibition and ARBs in patients with DN [105].

Ruboxistaurin, a protein kinase C (PKC)-beta inhibitor added to R-A system blockade therapy has also been shown to partially reduce HF in animal models [101], further illustrating the need for addressing multiple pathways to normalize GFR in hyperfiltering subjects. In clinical studies, when ruboxistaurin was administered to a small group of euglycemic, hyperfiltering patients, a significant reduction in GFR has been observed [106]. These results are based on the hypothesis that the haemodynamic changes seen in HF are mediated by protein kinase C (PKC)-β induced intracellular pathways.

COX-2 inhibition during clamped euglycaemic conditions has been demonstrated to result in partial resolution of HF in T1DM subjects but interestingly failed to have the same effect on the GFR increase mediated by short-term hyperglycaemia [44]. However, the long-term use of COX-2 inhibitors in humans is limited due to their adverse-effect profile [107].

C-peptide, a molecule that links the A- and B-chains of the insulin molecule in the insulin biosynthesis pathway has been shown to be a potential renoprotective agent due to its actions on glomerular efferent arterioles in experimental animal models [100]. C-peptide reduced diabetes-induced HF via a dilation of the efferent arteriole and inhibition of tubular Na reabsorption, both potent regulators of the glomerular filtration pressure. Thus, the administration of C-peptide could theoretically prevent glomerular HF, although clinical data supporting this proposed effect of C-peptide on HF is currently lacking [108].

Renal sympathetic innervation has been proposed to have an important role in mediating glomerular HF in experimental diabetes. In this regard, renal denervation has been shown to prevent glomerular HF in diabetic rats [102]. To date no clinical studies have investigated the possible role of renal sympathetic denervation on HF.

A reduction of levels of microalbuminuria as well as HF in diabetic patients in response to thiazolidinediones (TZDs) has been reported [98]. Rosiglitazone has been shown to ameliorate glomerular HF in patients with early T2DM, by means of improving nitric oxide bioavailability and amelioration of renal glomerular endothelial dysfunction as evidenced by the changes in filtration fraction. The resultant renal hemodynamic changes were correlated with a reduction in levels of microalbuminuria. A possible explanation of the above changes is that increased nitric oxide bioavailability lowers intraglomerular capillary pressure and filtration fraction, while recovery of the glomerular endothelium may have improved the properties of the filtration barrier. Whist, TZDs may have a protective agent in HF and early DN, and theoretically decrease renal end-organ damage in diabetes, to date, no long-term studies on whether TZDs can prevent the development of renal clinical endpoints have been performed.

The sodium-glucose co-transporter 2 (SGLT2) mediates high-capacity glucose uptake in the early proximal tubule, and SGLT2 inhibitors, via their ability to promote glycosuria, have been developed as glucose lowering medications. There is also an emerging body of evidence suggesting that this class of medication may have an important role in reducing GFR and hence, reversing HF, at least in the short-term, by counteracting the tubulo-glomerular feedback mechanism. In a recent, euglycaemic clamp study involving 13 normofiltering and 27 HF T1DM subjects, eight weeks of treatment with the SGLT-2 inhibitor empagliflozin resulted in a reduction of GFR of 33 mL/min/1.73m² in the HF group without any change in GFR in the normofiltering group [99]. A similar degree of GFR reduction associated with ACEIs was observed in previous studies of HF in young patients with uncomplicated T1DM. Apart from the above, SGLT-2 inhibitors may possibly have additional renal protective effects as they lower blood pressure and promote weight loss [109].

10. Conclusion

Potential mechanisms leading to renal HF in diabetes are not fully understood and several hypotheses have been proposed, including alterations in glomerular haemodynamic function and tubulo-glomerular feedback. A combination of hemodynamic, vasoactive, tubular, growth promoting and metabolic factors most likely contributes to the pathogenesis of HF.

The role of early HF as a predictor of microalbuminuria or the development of renal impairment (GFR<60 mL/min1.73m²) is uncertain. Inconsistencies of studies looking at this issue may relate to differences in GFR methodology, variable definitions of HF, inadequate duration of follow-up and many confounding factors such as duration of disease and lack of adjustment for blood pressure and metabolic control. The threshold GFR of definition of HF in those over the age of 45 years is further complicated by the age-related physiological decline in GFR.

One difficulty in examining the decline in renal function from a HF range to the normofiltration range without easy accessibility to serial renal biopsy data is the differentiation between resolution of HF, which is largely a functional and potentially beneficial process, from true nephron loss, which is irreversible and harmful.

In summary, the role of HF as a causative factor in renal disease progression is still unclear and warrants further prospective longer-term studies. Whether reversal of HF with therapeutic agents is protective against reducing the risk of development of albuminuria and renal impairment is also worth investigating in prospective randomized trials. Perhaps, in the future, a combination approach of targeting the multiple mechanistic processes involved in causing glomerular HF will lead to an effective strategy for resolving HF, which may be translated into improving long-term renal outcomes for people with diabetes.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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