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Diabetes & Metabolism 41 (2015) 5–17

Review

The impact of hyperfiltration on the diabetic kidney

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Received 4 April 2014; received in revised form 2 October 2014; accepted 2 October 2014
Available online 18 November 2014

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 longer-term 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/1.73m^2, 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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Keywords: Hyperfiltration; Diabetic kidney disease; Obesity; Metabolic syndrome; Vascular disease; Diabetic nephropathy

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 macroalbuminaemic 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/1.73m^2, 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

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http://dx.doi.org/10.1016/j.diabet.2014.10.003
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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 over-estimates 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 under-estimate high GFR values, especially for patients with diabetes [4–6]. Therefore direct measurements of GFR using clearance techniques with inulin, iohexol, isotopically 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 prostanoids.

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 been 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 prostanoids 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

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