Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension

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Keywords: diabetes; glomerular filtration rate; hypertension; kidney; renal

Glomerular hyperfiltration is a characteristic functional abnormality in insulin-dependent diabetes mellitus and occurs in the large majority of young Type 1 diabetic patients. Hyperfiltration is hypothesized to be a precursor of intraglomerular hypertension leading to albuminuria. Glomerular filtration rate (GFR) then falls progressively in parallel with a further rise in albuminuria which may lead, in the long run, to end-stage renal failure. Experimental and clinical studies have shown that glomerular hyperfiltration can occur also in hypertension. However, whether hyperfiltration occurs in early stages of hyperglycaemia and high blood pressure, such as in pre-diabetes and pre-hypertension, is not well known. In this issue of the Journal, Okada and Coll studied a large Japanese population showing that in pre-diabetic and pre-hypertensive subjects, the prevalence of hyperfiltration is proportional to the level of glucose and blood pressure, respectively. One main problem with the diagnosis of hyperfiltration is that no generally accepted definition is available due to the strong inverse correlation of GFR with age. To overcome this limitation, Okada et al. calculated the upper normal limit of GFR in a large healthy Japanese sample divided into 10-year age groups, providing age- and sex-specific reference values.

For hyperfiltration to develop, the concomitant action of a variety of pathogenetic factors are needed including increased body mass index, hyperinsulinaemia, activation of the sympathetic nervous system, hyperleptinaemia, increased oxidative stress, inflammatory cytokines, etc. Another mechanism accounting for increased GFR in obese persons is increased NaCl intake. In addition, a significant role of increased Na\(^+\) reabsorption in the pathophysiology of glomerular hyperfiltration in obesity and hypertension has been described. Pharmacological agents with action on the renin–angiotensin system are effective in reducing glomerular hypertension which accounts for their efficacy in preventing progression of microalbuminuria in diabetes and hypertension. According to current guidelines, only low GFR and microalbuminuria or proteinuria should be considered as markers of renal dysfunction. Due to the strong association between hyperfiltration and risk of microalbuminuria found in diabetes and hypertension, hyperfiltration should be regarded as a precursor of nephropathy in these clinical conditions. More extensive use of markers of early organ damage may help clinicians to reach a more timely decision about the initiation of treatment and thus delay cardiovascular complications. Hyperglycaemia and high blood pressure in people with hyperfiltration should be treated earlier to prevent the progression of renal dysfunction to chronic kidney disease.

Increased GFR, also called hyperfiltration, is a proposed mechanism for renal injury in several clinical conditions. According to the Brenner theory [1], low nephron number at birth explains why some individuals are prone to developing progressive renal damage later in life when other risk factors become operative. At the single-nephron level, hyperfiltration is hypothesized to be a precursor of intraglomerular hypertension leading to albuminuria. Increased glomerular capillary hydraulic pressure may be due to changes in systemic arterial pressure and/or changes in efferent and afferent arteriolar resistances. In the absence of therapeutic interventions, GFR then falls progressively in parallel with a further rise in albuminuria which may lead, in the long run, to end-stage renal failure (Figure 1). Human models of renal injury are in keeping with this pathogenetic view. Glomerular hyperfiltration has been observed in patients with unilateral renal agenesis [2], congenitally reduced nephron number [3] and acquired reduction in renal mass [4]. These individuals are prone to developing proteinuria early in life in association with glomerular sclerosis. It is suggested that this model of renal injury may apply to the early diabetic or hypertensive kidney.

Glomerular hyperfiltration in diabetes and hypertension

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Nephrol Dial Transplant (2012): Editorial Comments 1709

...showed a correlation with HbA1c [7]. However, the association between hyperfiltration and nephropathy was subsequently found to be independent of metabolic control. Amin et al. [5] in a prospective cohort of children with Type 1 diabetes demonstrated that glomerular hyperfiltration may be predictive of microalbuminuria independent of HbA1c level. Some studies have shown that glomerular hyperfiltration occurs also in hypertension. In animal models of salt-dependent hypertension, hyperfiltration has been shown to be associated with a faster decline in renal function as it precedes and hastens the development of glomerulosclerosis [8]. Glomerular hyperfiltration has been shown to occur in humans in the early stage of hypertension during sympathetic nervous system activation [9]. In addition, Schmieder et al. [10] observed that hyperfiltration was associated with early target organ damage in hypertensive patients. In a longitudinal study, the same group of investigators found that glomerular hyperfiltration was associated with an increase in serum creatinine during a 6-year follow-up of 88 hypertensive patients [11]. In that study, a high creatinine clearance emerged as a clinical diagnostic marker of early hypertensive nephropathy whereas an elevated protein excretion (between 200 and 500 mg/day) was not predictive of outcome. More recently, in a cohort of 502 young-to-middle-age Stage 1 hypertensive subjects from the HARVEST study, Palatini et al. [12, 13] found that GFR adjusted for many confounders was a strong independent predictor of final urinary albumin after 8 years of follow-up. Patients with hyperfiltration had an adjusted hazard ratio for development of microalbuminuria based on at least one positive measurement of 4.0 [95% confidence interval (95% CI) 2.1–7.4, P < 0.001] and an adjusted hazard ratio for development of microalbuminuria based on two consecutive positive measurements of 4.4 (95% CI 2.1–9.2, P < 0.001), as compared with patients with normal filtration [12].

**Glomerular hyperfiltration in pre-diabetes and pre-hypertension**

Whether hyperfiltration occurs also in early stages of hyperglycaemia and high blood pressure, such as in pre-diabetes and pre-hypertension, is unclear. As stated above, increased GFR represents an early and potentially reversible stage of renal dysfunction, and thus identifying subjects with glomerular hyperfiltration among those with pre-diabetes or pre-hypertension might be helpful for implementing preventive and therapeutic strategies. In this issue of the Journal, Okada and Coll [14] provide important novel information in this regard. These authors studied 99 140 Japanese people (54 547 males and 44 593 females) aged 20–89 years. GFR was estimated from serum creatinine, using a modified Modification of Diet in Renal Disease equation adapted for Japanese people. The authors found no clinically important differences between subjects with hyperfiltration and those with normal filtration except for fasting blood glucose level. At variance, subjects with hyperfiltration were older males with higher uric acid, dyslipidaemia and proteinuria as compared with subjects with normal filtration. In both pre-diabetic and pre-hypertensive subjects, the prevalence of hyperfiltration increased with increasing stage of the disease. The adjusted risk of hyperfiltration was 1.29, 1.58 and 2.47, respectively, for Stage 1 pre-diabetes, Stage 2 pre-diabetes and diabetes (P for trend <0.001) and was 1.10, 1.33 and 1.52, respectively, for Stage 1 pre-hypertension, Stage 2 pre-hypertension and hypertension (P for trend <0.001). These data are in keeping with recent results by Melson et al. [15] obtained in middle-aged subjects without diabetes. In this population, impaired fasting glucose was associated with hyperfiltration independent of age, sex, body mass index, blood pressure, smoking status and insulin levels. The above findings indicate that in people with pre-diabetes or pre-hypertension, GFR should be monitored carefully to identify subjects with hyperfiltration who might be at increased risk for subsequent kidney damage.

**Identification of subjects with hyperfiltration**

One main problem with the diagnosis of hyperfiltration is that no generally accepted definition is available for this clinical entity. The main reason why the levels of GFR that represent hyperfiltration are not clearly defined is that they are heavily dependent on age [16] (Figure 2). In a longitudinal study series of renal function in Type 2 diabetic patients with a mean age of 62, the overall rate of decline of GFR was −1.34 mL/min/year over 3.5 years [17] and −1.2 mL/min/year over 5.5 years [18], with similar rates...
in normo- and micro-albuminuric subjects. Thus, a GFR of 120–149 mL/min/1.73 m² may be considered normal in young adults (<30 years), in whom a level that exceeds 150 mL/min/1.73 m² may reflect hyperfiltration [19]. According to this definition, 20% of the HARVEST participants (mean age 33 years) exhibited hyperfiltration at enrolment [12]. At variance, a GFR of 120–149 mL/min/1.73 m² may represent hyperfiltration in the elderly, in whom a GFR of 60–89 mL/min/1.73 m² is considered to be normal according to the Kidney Disease Outcomes Quality Initiative guidelines [19]. To overcome this limitation, Okada et al. [14] calculated the upper and lower normal limits of GFR in 30,426 healthy Japanese subjects divided into 10-year age groups. Hyperfiltration was defined as estimated glomerular filtration rate (eGFR) above the age- and sex-specific 95th percentile for healthy subjects, while hypofiltration was defined as eGFR below the 5th percentile. In both genders, we found that the upper normal level of GFR progressively declined with age, going from the youngest (20–29 years) to the oldest (70–89 years) group. Although these data provide reference values stratified by age and gender, which may be helpful for identifying subjects with true hyperfiltration, one should be aware that they apply only to Asian populations and may not be extrapolated to other ethnic groups. In fact, relationships of GFR with age and other clinical variables have been reported to vary somewhat by ethnicity. A higher prevalence of hyperfiltration has been reported in certain ethnic groups, such as Pima Indians, African-Americans, Asians and Polynesians, than in Caucasians [16, 20] although published, direct ethnic comparisons within a study have been limited to non-Hispanic Whites and blacks [21].

Other factors affecting GFR

Although hyperfiltration is more common in pre-diabetes and pre-hypertension than in healthy subjects, the stimuli provoking such changes in the early diabetic or hypertensive kidney are unclear.

Among the Japanese people evaluated by Okada et al. [14], only a minority exhibited a GFR typical for hyperfiltration. This suggests that for hyperfiltration to develop, the concomitant action of a variety of pathogenetic factors is needed. Among these, increased body mass index ranks as a major determinant of glomerular hyperfiltration both in diabetic and hypertensive patients [22, 23]. In the young hypertensive participants from the HARVEST study, we observed a progressive increase in GFR with increasing body mass index (Figure 2). In the HARVEST subjects with obesity, age- and sex-adjusted GFR was 165.3 ± 5.1 mL/min/1.73 m², whereas in normal weight subjects, it was 119.3 ± 1.7 mL/min/1.73 m² (P < 0.0001) (unpublished observations). This suggests that the kidneys of obese people are more susceptible to the adverse effects of elevated blood pressure than the kidneys of normal weight subjects. However, there is increasing evidence that obesity contributes to the development and progression of chronic kidney disease also in subjects without hypertension or diabetes [22, 23]. Recently, glomerular hyperfiltration was demonstrated in a large cohort of young men to be associated with elevated body mass index and an unfavourable metabolic profile [24]. Conversely, Chagnac et al. [25] demonstrated that in subjects with severe obesity, weight loss resulted in a decrease in GFR, renal plasma flow and filtration fraction. Several mechanisms have been proposed to explain these altered renal haemodynamic indicators in obesity, including hyperinsulinaemia, hyperleptinaemia and activation of the sympathetic nervous system [22]. Indeed, bilateral renal denervation has been shown to normalize glomerular hyperfiltration in diabetic rats, indicating that sympathetic nerve stimulation is involved in the induction of glomerular hyperfiltration [26]. Another important mechanism leading to hyperfiltration in diabetes and obesity is oxidative damage to lipids and proteins [27, 28]. Increased oxidative stress has been described in
young Type 1 diabetic patients, which was linked to the presence of hyperfiltration [29]. Glomerular hyperfiltration is often present also in the metabolic syndrome, which is a well known risk factor for chronic kidney disease [27]. Recent results obtained by Li et al. [27] in a swine model showed that increased GFR in early metabolic syndrome was associated with renal adiposity and microvascular proliferation, which involved mainly the renal cortex and preceded significant activation of oxidative stress and inflammation. Using the diabetic Zucker fatty rat as a model of metabolic syndrome, Kuwabara et al. [30] demonstrated that increased oxidative stress induces deterioration of the glomerular endothelial surface layer, which is composed of large amounts of glycoprotein, such as heparan sulphate proteoglycan. The decrease in thickness of the endothelial surface layer, partly mediated by increased heparanase levels, was associated in this model to an increase in vascular permeability and onset of albuminuria. Oxidation of low-density lipoprotein, commonly observed both in obesity and chronic kidney disease, also stimulates synthesis of angiotensin II, which in turn increases transforming growth factor-β and plasminogen activator inhibitor-1, thereby favouring the progression of glomerular fibrosis [31, 32].

Increased cardiac output in obesity is an adaptive mechanism to supply adequate perfusion to an increased tissue mass [23]. The number of nephrons does not increase with weight gain in adult individuals, thus elevated renal plasma flow increases single-nephron perfusion. This results in increased intracapillary glomerular pressure and hyperfiltration, thereby starting the process that ultimately leads to GFR decline [33]. Other factors may also contribute to the initiation and/or exacerbation of renal dysfunction in obese individuals. In particular, inflammatory cytokines, h-C-reactive protein, adipokines and circulating free fatty acids, have been associated with glomerular hyperfiltration and renal injury [22, 34]. Another mechanism accounting for increased GFR in obese persons is increased NaCl intake. Several investigators have reported that salt intake increases GFR in white patients with uncomplicated hypertension [22, 35]. In a group of patients with mild hypertension, Mallamaci et al. [36] found that GFR was significantly higher at high salt intake (125 +/- 10 mL/min) than at habitual (113 +/- 7 mL/min) and at low salt intake (97 +/- 6 mL/min). On aggregate, urinary salt excretion was significantly related with the GFR and the slope of this relationship predicted that a 100 mmol/day increase in salt intake was associated with a 14.6 mL/min rise in the GFR. The GFR response to salt loading was largely independent of the renin–angiotensin–aldosterone (RAA) system [36]. Increased salt intake reportedly induces a renal vasoconstrictor response with a reduction of renal blood flow and an increase of filtration fraction in salt-sensitive, but not in salt-resistant, hypertensive African-Americans [37]. In addition, a significant role of increased Na⁺ reabsorption in the pathophysiology of glomerular hyperfiltration in obesity and hypertension has recently been described [38]. The role of the RAA system as a causative factor for hyperfiltration in diabetes or obesity is controversial. According to some authors, the activation of the RAA system contributes to the progression of renal damage in diabetes and obesity [22, 34]. Obese subjects have increased RAA system activity leading to increased proximal sodium reabsorption [39] and to an increment of blood pressure, which may accelerate the progressive deterioration of renal function over time. At variance, Carvalho-Braga et al. [40] in insulin-dependent diabetic patients observed that glomerular hyperfiltration was not causally related to hyperactivity of the RAA system. A variety of other hormonal factors may influence hyperfiltration, including atrial natriuretic peptide, endothelial-derived relaxing factor, prostaglandins, thromboxanes, kinins, cyclooxygenase-2 and protein kinase C-b [16, 34, 41]. More recently, hyperfiltration has been associated with peripheral vascular alterations, including low arterial stiffness and endothelial dysfunction [42]. It has therefore been suggested that the hyperfiltration stage reflects generalized microvascular and macrovascular functional changes [41, 42]. According to the ‘tubular hypothesis’, glomerular hyperfiltration may stem from primary effects on the proximal tubule impacting on glomerular filtration, by tubuloglomerular feedback via the macula densa [43]. According to this tubulocentric view, glomerular hyperfiltration and higher proximal reabsorption of sodium may result in accelerated loss of kidney function and hypertension in diabetics. Cigarette smoking has been reported to be associated with elevated GFR in cross-sectional analyses and with renal deterioration in longitudinal studies [22]. In a recent longitudinal study of 10 118 Japanese men aged 40–55 years without proteinuria or renal dysfunction at entry, current smokers had a 1.32-time higher risk for the development of glomerular hyperfiltration and a 1.51-time higher risk for proteinuria than non-smokers [44]. The mechanisms by which smoking induces hyperfiltration, progressive renal disease and cardiac complications are still elusive. However, increasing evidence suggests that oxidative stress and inflammation play a critical role in the mechanism for the pathophysiological link between smoking and organ damage [45]. An interaction between serum from active smokers and inflammatory cytokines that causes endothelial dysfunction has been shown by Barbieri et al. [46]. Among 649 healthy subjects, Sauri-sari et al. [47] found a high eGFR and a high urinary protein level in smokers, which were associated with an increase in highly sensitive C-reactive protein. The role of cardiac NADPH oxidase and antioxidant enzyme system on ventricular remodelling induced by tobacco smoke was recently investigated by Rafacho et al. [48] in Wistar rats. After a 2-month exposure to tobacco smoke, the myocyte cross-sectional area and left ventricle end-diastolic dimension were increased by 16.2 and 33.7%, respectively, compared to the controls, with a decrease in the ejection fraction and fractional shortening. These alterations were related to augmented heart oxidative stress, which was characterized by an increase in NADPH oxidase activity, increased levels of lipid hypox- peroxide and depletion of antioxidant enzymes, suggesting that this pathway plays a role in the ventricular remodelling induced by exposure to tobacco smoke [48]. Although our understanding of the relative contribution of risk factors implicated in hyperfiltration is still
limited, evidence derived from clinical series in patients with elevated glycaemia or high blood pressure supports the hypothesis that several important factors act synergistically with diabetes and hypertension to promote the progression and perhaps even the initiation of chronic kidney disease.

Therapeutic considerations

It has been demonstrated that lowering blood pressure while maintaining increased glomerular pressure and flow does not protect against renal injury, whereas normalization of glomerular pressure delays renal dysfunction, despite persistence of hyperfiltration [49]. Pharmacological agents with action on the RAA system are effective in reducing glomerular hypertension and decelerating deterioration of renal function and structure in a variety of rodent models of renal injury [28, 50]. This may explain their efficacy in preventing progression of microalbuminuria in diabetes and hypertension. Several mechanisms can account for the favourable effect of RAA system inhibition in subjects with glomerular hyperfiltration. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) suppress heparan sulphate expression and preserve heparan sulphate proteoglycan from degradation [30]. Angiotensin II is known to directly induce expression of NADPH oxidase components and enhance reactive oxygen species (ROS) generation [30]. ARBs decrease ROS production and activate the antioxidant defence system [30]. In a rat model of metabolic syndrome, irbesartan proved effective in preventing deterioration of the endothelial surface layer and suppressed albuminuria [30]. Findings from several observational studies indicate that phosphate might have an independent pathogenic role in the onset and progression of chronic kidney disease [51]. The Ramipril Efficacy In Nephropathy (REIN) study showed that the renoprotective effect of ramipril decreased as serum phosphate increased, suggesting that a high phosphate burden may decrease the renoprotective effect of ACE inhibitor therapy in patients with proteinuric chronic nephropathies [51]. These findings suggest that serum phosphate might be a specific target for renoprotective therapy in patients with chronic kidney disease and treatment with phosphate-binding agents may serve to optimize the renoprotective effect of ACE inhibition. Thus, blockade of the RAA system with ACE inhibitors or ARBs should be used in diabetic or hypertensive patients with glomerular hyperfiltration especially in subjects with obesity. In a post hoc analysis of the REIN trial, reduction of end-stage renal disease with ramipril was much higher among the obese patients (86%) than among those with overweight or with normal weight (incidence rate reduction of 45 and 42%, respectively) [52]. Attenuation of hyperfiltration can be obtained with other pharmacological means that might slow down the development and progression of chronic renal failure. Skott et al. [53] have shown that acetazolamide, a proximally acting diuretic that activates tubuloglomerular feedback by increasing solute delivery to the macula densa, can decrease glomerular hyperfiltration by 18% in normal humans. To test the hypothesis that this decrease in hyperfiltration is specific to acetazolamide and is not due to a nonspecific diuretic effect, a clinical trial in subjects with severe obesity has recently been started with the aim of comparing the effects of furosemide and acetazolamide on glomerular haemodynamics (http://clinicaltrials.gov/ct2/show/NCT01146288).

Conclusions

In patients with diabetes or a history of cardiovascular or renal disease, current guidelines recommend drug treatment to be initiated below the 140/90 mmHg level, between 130 and 139 mmHg for systolic blood pressure and between 85 and 89 mmHg for diastolic blood pressure. The 2007 European guidelines classify hypertensive patients with subclinical target organ damage among those with a high total cardiovascular risk [54]. A body of evidence indicates that in hypertensive individuals, renal subclinical organ damage is associated with increased 10-year risk of cardiovascular events [54]. In the same guidelines, only low GFR and microalbuminuria or proteinuria are considered markers of reduced renal function. Up to now, glomerular hyperfiltration has not been included among the risk factors for renal dysfunction. However, considering the strong association between hyperfiltration and risk for development of microalbuminuria found in diabetes and hypertension, hyperfiltration should be regarded as a precursor of nephropathy in these clinical conditions. In medical practice, anti-hypertensive treatment is often deferred until overt organ damage occurs, when complete reversibility is difficult to achieve. More extensive use of markers of early organ damage may help clinicians to reach a more timely decision about the initiation of treatment and thus delay cardiovascular complications. As suggested by Okada et al. [14] in their article, hyperglycaemia and high blood pressure in people with hyperfiltration should be treated earlier to prevent the progression of renal dysfunction to chronic kidney disease. Oxidative stress to proteins and lipid peroxidation may damage the renal glomerulus during the first few years of the disease. Pharmacological interventions and strict glycaemic and lipid control should thus be implemented early together with a diet with sufficient intake of foods rich in antioxidants [29].

Conflict of interest statement. None declared.

References


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*Received for publication: 21.12.11; Accepted in revised form: 20.1.12*