Title

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Abstract It is generally believed that significant renal ablation leads to hyperfiltration and eventually progressively worsening chronic kidney disease. The data behind this belief have not been scrutinized intensively. More importantly, the above belief leads many physicians to manage patients differently than they otherwise would manage. Here, we examine the data behind whether hyperfiltration occurs when patients lose kidney mass (by excision or by disease) and whether the hyperfiltration is uniformly injurious.

Keywords Renal ablation · Hyperfiltration · Chronic kidney disease

How it is we come to believe in hyperfiltration injury?

It is common belief that at least in rats if one performs 5/6th nephrectomy, the remaining portion of the kidney will progressively undergo fibrosis and scar formation despite being normal right after the surgery. Nephrologist and other physicians have often extended the above belief into humans in their routine patient care. In 1932, Chanutin and Ferris removed about 2/3rd of both kidneys from the Munich–Wistar strain of albino rats by ligating 2 poles of both kidneys 1 week apart and then followed the serum non-protein nitrogen levels (mainly urea) over time [1].

They found that the non-protein nitrogen levels continued to increase in a majority of rats in spite of no further insults to the remaining kidneys. In the majority of partially nephrectomized rats, characteristic features included progressive development of polyuria, albuminuria, nitrogen retention and hypertension and the presence of hypertension was associated with decline in kidney function. More recently in 1975, Shimamura and Morrison performed 5/6th nephrectomy in the adult male Munich–Wistar rats and documented the pathological changes seen over time [2]. By 10 weeks, they found increase in glomerular size and hypertrophy of the visceral glomerular epithelial cells. At 25 weeks, the glomeruli started to undergo hyalinization which continued to worsen by 50 weeks. Mesangial matrix accumulation and occlusion of capillary lumina and Bowman's space followed, resulting in obsolescent glomeruli. The authors wondered whether the pathological changes seen were the result of glomerular hyperfiltration and stated that it is the most likely cause. Despite the pathological changes, renal function remained compensated for many months in these rats.

Juxtamedullary nephrons versus superficial nephrons

It is common knowledge that juxtamedullary nephrons are usually the nephrons that are most prone to damage. This is thought to be due to the fact that since these are the nephrons closest to the main renal arteries, they are exposed to the highest pressures. As a result of the high pressures, these nephrons are least able to autoregulate and most prone to hypertensive injury. The fact that the juxtamedullary nephrons are usually the most easily damaged suggests that hypertensive injury is likely playing a more

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significant role than that due to hyperfiltration (which is probably more evenly distributed). Recently, one group found hyperfiltration injury was only confined to a sub-population of nephrons in spontaneously hypertensive rats, and it did not cause tubular atrophy [3]. They concluded that even though hyperfiltration injury does lead to progressive chronic kidney disease, it does not contribute to it as much as previously thought.

How to prevent hyperfiltration injury in rats?

Using micropuncture technique, Hostetter et al. studied glomerular capillary pressure and single nephron GFR in the male Munich–Wistar rats [4]. The experimental group (group 2) underwent right nephrectomy and segmental infarction of 5/6th of the left kidney (11/12th nephrectomy). A third group of rats (group 3) had the same procedure but then were fed a low-protein diet. In this study, it was found that group 2 rats developed increases in the glomerular capillary pressure and single nephron GFR, while group 3 rats were spared the damage. The authors concluded that glomerular damage occurs as a result of an increase in glomerular capillary pressure from hyperfiltration. In addition, they speculated that not only the glomerular damage is due to the worsened hypertension seen in the group 2 rats, but also protein restriction protects against these changes by decreasing hyperfiltration. The above findings were subsequently confirmed with a more detailed pathological study [5].

Other than protein restricted diet, angiotensin converting enzyme (ACE) inhibitor therapy has also been shown to prevent glomerular injury in rats. In 1986, Anderson et al. compared the effects of enalapril with those of triple antihypertensive regimen of reserpine, hydralazine, and hydrochlorothiazide again in the male Munich–Wistar rats [6]. With micropuncture studies, they found similar lowering of systemic blood pressure in 5/6th nephrectomized rats in both antihypertensive groups. Glomerular capillary pressure remained elevated in the triple antihypertensive group but not in the enalapril treated animals, while single nephron GFR was lowered in both antihypertensive treated groups similarly. Although there were no sham-operated rats in this study, single nephron GFR was clearly elevated even in the enalapril treated rats compared to the sham-operated animal in their previous study [4], indicating that hyperfiltration was still present even in the enalapril treated rats. While only enalapril was able to prevent glomerular injury, GFR was maintained in all treatment groups up to 18 weeks post-surgery despite the glomerular damage on pathology.

The blood pressure independent effects of ACE inhibitors in preventing glomerular damage have not been universally observed in rat studies. In 1994, Griffin et al. performed 5/6th nephrectomy in the male Sprague–Dawley rats using surgical nephrectomy in one group of rats and infarction-induced nephrectomy in another group of rats [7]. They found systemic hypertension (measured by radiotelemetric method) only in the group that had nephrectomy by infarction, and these were the only rats which developed proteinuria and glomerulosclerosis and the degree of glomerulosclerosis directly correlated with the systemic blood pressure. Interestingly, they found autoregulation to be impaired in all rats with reduced renal mass. Subsequently, they did micropuncture studies again on male Sprague–Dawley rats and found rats which had 5/6th nephrectomy by surgical ablation had similar single nephron GFR as infarction-induced 5/6th nephrectomy, lower systemic blood pressures and somewhat lower glomerular capillary pressures [8]. In summary, it is shown that in most cases glomerular injury in rats can be significantly attenuated by low-protein diet, blood pressure control and ACE inhibition despite the continued presence of significant hyperfiltration.

Furthermore, in an interesting study in rats, Yoshida et al. had three groups of rats [9]. First group had uninephrectomy and ligation of blood supply to 2/3rd of the other kidney. Second group also had 2/3rd ligation of one kidney but instead these rats had ureteral diversion into the peritoneal cavity. Last group of rats was the controls with a sham operation. Both the first and second group of rats had hyperfiltration and increased glomerular pressures, but only the first group had hypertrophy and sclerosis. The authors thus demonstrated dissociation between hyperfiltration and injury.

Where do humans fit in the spectrum of hyperfiltration?

It appears that the degree of hyperfiltration-induced renal injury varies among animal models. As mentioned earlier, five-sixth partial nephrectomy of Munich–Wistar rats incurs multiple renal injuries, including albuminuria, nitrogen retention, polyuria, and hypertension [1]. Hypertension associated with cardiac hypertrophy as well as polyuria, albuminuria, and renal insufficiency was reproduced in many of three-fourth nephrectomized dogs [1, 10]. Cachexia ending in death ensued in three-quarters of nephrectomized cats without necessarily polyuria or persistent albuminuria [11, 12]. There is a mouse strain (C57B16), which does not develop hypertension, significant proteinuria, or accelerated glomerulosclerosis despite extensive renal mass reduction even though glomeruli enlarge and hyperfiltration were observed [13]. Clearly, different species have varying amounts of kidney injury

from hyperfiltration. Determining where humans fit in the spectrum of hyperfiltration injury will help us to better understand humans with chronic kidney disease and to better manage patients.

Based on studies in animal models, intraglomerular hypertension, and glomerular hyperfiltration are early findings shared in the clinical course of multiple disease states and, therefore, thought to be important factors in the progression of renal disease to chronic kidney disease. Whether these observations made in animal models can be extended to humans will play an important role in guiding the management and consultation of patients with hyperfiltration-related renal pathologies, such as living kidney donors, nephrectomy patients, and diabetic patients.

Why it is important?

To illustrate the importance of the belief in existence of hyperfiltration injury in routine patient care, we will outline case reports of two similar patients with lupus nephritis who were managed differently.

Case 1

A 58-year-old woman with history of lupus diagnosed at the age of 14 and medically controlled chronic hepatitis B presented to a regional hospital with nephrotic range proteinuria in April 2002 and underwent kidney biopsy that revealed Class V lupus nephritis. She was started on prednisone and plaquenil. Her creatinine remained around 1.0 mg/dL until March of 2005 at which time her prednisone was completely stopped. In May of 2005, her creatinine was 2.1 mg/dL, and urinalysis was significant for 3+ protein, and 3+ blood. Kidney biopsy at that time showed class IV lupus nephritis. She was pulsed with salumedrol and received 5 doses of IV cyclophosphamide monthly. However, in October 2005, she had an episode of pneumonia, and as a result, cyclophosphamide was discontinued, at which time creatinine was 1.36 mg/dL, down from a peak of 2.85 mg/dL in June of 2005. Four years later in December 2009, she was taking azathioprine 25 mg/day and prednisone 5 mg/day, at which time serum creatinine was 2.72 mg/dL. In February 2010, her lupus was thought to be of low grade activity, as ANA titer was 1:640, and C3 was 70 which had been unchanged for many years. Azathioprine was briefly increased to 75 mg daily by nephrology service before it was reduced to 25 mg/day a week later by rheumatology service. In April 2010, renal biopsy was performed to evaluate the need to titrate up her immunosuppressive regimen. Serum creatinine was about 2.5 mg/dL. Biopsy sample was limited with four fully, two

partially sclerosed glomeruli, and two glomeruli with mild mesangial and endocapillary proliferation. There was severe chronicity of the tubulointerstitium as well as focal areas of acute tubulointerstitial inflammation. Because of the degree of chronicity of pathological findings and consideration that the remaining glomeruli will not survive for long because of hyperfiltration injury in any case, the immunosuppressive therapy was kept at azathioprine 25 mg daily and prednisone 5 mg daily. Consequently, in May 2012, she developed uremic symptoms with creatinine of 5.5 and shortly started dialysis. Her blood pressure remained well controlled throughout the entire course of her illness.

Case 2

A 55-year-old woman was diagnosed with lupus at the age of 25. Kidney biopsy revealed class V lupus nephritis during a hospitalization in 1994 for active lupus. She was treated with prednisone and received six doses of cyclophosphamide and maintained on azathioprine 100 mg daily and prednisone 10 mg daily. In 2003, she was diagnosed with diabetes at which time her creatinine was 2.3 mg/dL. In June 2004, she developed significant proteinuria and hematuria, and her creatinine had gone up to 3.7 mg/dL. ANA titer was >1:160, dsDNA was highly positive, and C3 and C4 were 36 and 11, respectively. Renal biopsy revealed that 16 out of 26 glomeruli were completely sclerosed. The other glomeruli showed diffuse proliferative endocapillary proliferation with evidence of advanced chronic tubule-interstitial scarring. In this case, even though the biopsy again demonstrated severe chronic disease, she was treated with pulse steroids and subsequently oral prednisone and oral cyclophosphamide for 2 months. After 2 months, cyclophosphamide was changed to azathioprine 100 mg daily and switched again to mycophenolate in 2009. In August 2012, her serum creatinine was 1.9 mg/dL, C3 and C4 were normal, and ANA had become negative. Her blood pressure also remained well controlled throughout the course of her illness.

In summary, the first patient was assumed to have end-stage kidney disease with significant elevation of serum creatinine but still far from needing dialysis. The patient was not treated adequately enough and need for dialysis arose in 2–3 years. On the other hand, despite kidney biopsy confirming almost end-stage kidney disease, the second patient was treated aggressively for active lupus nephritis as hyperfiltration injury was not considered to be an important factor. As a result, the patient avoided dialysis even several years later with a significantly elevated serum creatinine but far from needing dialysis.

Does hyperfiltration exist?

In rats, partial nephrectomy leads to compensatory hyperfiltration of the remaining nephrons in which the magnitude of increase in the glomerular filtration rate correlates with the amount of reduction in renal mass [4]. In an above-mentioned study of Munich–Wistar rats, the glomerular filtration rate, measured by inulin clearance, was 1.7 mL/min (14 days post-surgery) in the sham-operated rats, while GFR of those subjected to approximately 90 % (11/12th) nephrectomy was 0.41 mL/min (7 days post-surgery), 241 % of the expected post-nephrectomy GFR of 0.17 mL/min [5]. Similarly, in a study of kidney donors, glomerular filtration rates, measured by creatinine clearance, prior to and after uninephrectomy were 103 and 80 mL/min, respectively [14]. While renal mass was halved after uninephrectomy, the glomerular filtration rate increased to 160 % of the expected GFR. In both species, compensatory hyperfiltration following the renal mass reduction was observed well above the expected level given the degree of resection (Table 1). Thus, it seems hyperfiltration after renal ablation occurs without doubt and is likely universal with any significant degree of renal mass reduction.

The case against hyperfiltration injury

Kidney donors

Short-term studies of living kidney donors have demonstrated that compensatory hyperfiltration takes place early after nephrectomy, reaching 70–78 % of the preoperative glomerular filtration rate within days to weeks [14–16]. Thus, long-term follow-up of these donors provides a unique opportunity to examine the effects of hyperfiltration on the reduced renal mass. In 1983, Vincenti et al. looked at twenty kidney donors who underwent uninephretomy with a mean follow-up period of 15.8 years [14]. At 14–18 years after nephrectomy, they observed no significant change in blood pressures, and mean creatinine clearance was 78 % of the preoperative value. In addition, all except for two donors had protein excretion less than 200 mg/day, majority of which is non-albumin protein. Of note, the patient with the most severe proteinuria developed biopsy-confirmed glomerulonephritis after donating a kidney to her HLA-identical sister. The same author noted that the mean urine albumin excretion excluding the patient with proteinuria was similar to that of age- and gender-matched healthy controls. While the cause of proteinuria was not clear, no correlation between the severity of the proteinuria and the duration of time following transplantation was found. Nevertheless, renal function and blood pressure remained stable after 16 years of compensatory hyperfiltration in these twenty donors. Recently, much larger cohorts of donor population have been followed, and their risk of developing end-stage kidney disease was studied more thoroughly. Here, the two recently published studies consistently report approximately tenfold increase in the risk of end-stage kidney disease among donors compared to matched healthy non-donors with median follow-up periods of 8 and 15 years, respectively [17–19]. However, the absolute risk in these carefully selected healthy donors were small at less than 1 % and still much lower than the recently estimated risk of 3.6 % in the general population [20]. How much hyperfiltration injury versus reduced renal reserve plays a role in the higher risk of end-stage kidney disease in these donors is not clear but clearly despite the significant degree of hyperfiltration, the risk of end-stage kidney disease is still fairly small. In addition, familial factors may be in play here as most donors come from families of patients who have kidney disease.

Congenital solitary/mono-functioning kidney

In 2009, Sanna-Cherchi and colleagues looked at 312 patients with congenital anomalies of the kidney and urinary tract [21]. By 30 years of age, 58 (18.6 %) had started dialysis. This rate is much higher than in the highly selected kidney donors and clearly the general population. However, a significant difference in prognosis was observed based upon the category causing the congenital anomaly. This fact suggests that factors other than hyperfiltration contributed to the worsening of renal function as hyperfiltration should have been universally present.

In 2011, the KIMONO study was published looking at 206 children with solitary functioning kidney [22]. They

Table 1 Pre- and post-nephrectomy GFRs and calculated percentages of hyperfiltration in rats and humans

	Remnant kidney (rats) [4]	Unilateral nephrectomy (humans) [13]
Degree of resection (%)	90	50
GFR (whole kidney) (mL/min)	1.7 (sham-operated group)	100
GFR (post-nephrectomy) (mL/min)	0.41	80
GFR (expected) (mL/min)	0.17	50
% Hyperfiltration (%)	241	160

found presence of renal injury defined as hypertension and/or albuminuria and/or use of renoprotective medications in 32 % of the children at a mean age of 9.5. The significance of this finding is limited as renal injury was defined loosely, and in fact, the mean eGFR of patients with primary solitary kidney was 96 mL/min, and the mean eGFR of patients with secondary solitary kidney was 92 mL/min at 18 years of age. In any case, the authors postulated that the difference in renal prognosis between adult kidney donors and children with congenital anomalies may reflect differences in hyperfiltration injury between adults and children.

Finally, most recently, 79 survivors of Wilm's Tumor were retrospectively looked at to analyze long-term solitary kidney function [23]. At 15 years, 23 % of the patients showed signs of renal injury. In this study, lower eGFR was associated with treatment with unilateral nephrectomy, radiation therapy to the abdomen, use of cisplatin and ifosfamide. Overall with these studies, it is very hard to tease out the role for hyperfiltration injury as many other factors may have played a role in progressive renal dysfunction. It is possible children are more prone to hyperfiltration injury, but we are very far from having proved this concept.

Case reports

Some have postulated that there exists a critical level of renal mass beyond which hemodynamic changes will take place to produce functional and structural renal injury as described in rats, the critical level being one-fifth of normal GFR or 30 mL/min/1.73 m^2 as defined by Mitch et al. in 1976 and Heaf et al. in 2011, respectively [24, 25]. Interestingly, Rutsky et al. reported a case in which a 36-year-old man with no known renal disease suffered a traumatic injury to the lower back, resulting in ablation of four fifths of the functional renal mass [26]. Over the follow-up period of 10.8 years, serum creatinine averaged 2.1 ± 0.05 mg/dL, and creatinine clearance increased from 16 mL/min (38 days post-injury) to 57 mL/min (129 months post-injury). While 24-h urine protein differed significantly between the first 90 months (146 mg/24 h) and the last 40 months (426 mg/24 h) of follow-up, no evidence of linear or nonlinear increase was observed over the respective time periods. Unlike the kidney donor study mentioned above, 80 % of the urinary protein was found to be albumin [14]. Despite proteinuria, patient did not develop progressive glomerulosclerosis or chronic kidney disease despite significant reduction in renal mass.

Results presented in the above case report were later supported by several retrospective studies. In 1991, Foster et al. identified 13 patients with a remnant kidney who underwent surgical resection (they all had 2/3rd to 5/6th

nephrectomies) and had greater than 5 years of follow-up from 13 different centers [27]. Twelve had renal cancer and one had tuberculosis as indications for nephrectomy. Six patients were followed postoperatively for more than 10 years and all had stable serum creatinine less than 3.0 mg/dL (two were followed post-operatively for 25 and 30 years). Six of the seven patients with 5–7 years of follow-up had stable serum creatinine less than 3.0 mg/dL, while the seventh patient had increasing serum creatinine level at 4.1 mg/dL. Thus, only one out of the 13 patients had worsening kidney function over long period of follow-up despite having had only minimal kidney tissue remaining.

In the same year, Novick et al. studied long-term renal function in 14 patients with a solitary kidney who had undergone partial nephrectomy of their only kidney for renal cancer [28]. All patients had normal preoperative blood pressures, including those with a history of hypertension controlled without ACE inhibitors. Twelve patients had stable renal function based on serial serum creatinine over follow-up period of 5–17 years (mean 7.7 years), and two developed end-stage renal failure. Renal biopsy in four patients with moderate-to-severe proteinuria revealed focal segmental glomerulosclerosis (three patients) and global glomerulosclerosis (one patient).

In another study, improved renal function, reflected by positive slope of the reciprocal of the serum creatinine concentration ($1/S_{Cr}$) versus time, was demonstrated in hypertensive nephrosclerotic patients treated with minoxidil (+0.0031) versus Enalapril (+0.0025), while the glomerular filtration rate were increased by 48 % with minoxidil (38 mL/min) versus Enalapril (26 mL/min) [29]. Because minoxidil improved renal function while causing a relative hyperfiltration, the authors concluded that glomerular hyperfiltration is an unlikely mechanism for the progression of hypertensive nephrosclerosis. Results from the aforementioned studies indicate that hyperfiltration takes place early following the removal of renal mass due to kidney donation, trauma, or renal disease. Most patients maintain stable serum creatinine without worsening of renal function. They are, however, at risk for developing proteinuria, the extent of which is inconsistent amongst studies.

MDRD study

The protective effects of protein restriction and hypertension control against the progression of renal disease seen in rats sparked the Modification of Diet in Renal Disease (MDRD) study [30]. In part of this study, 585 patients with glomerular filtration rates of 25–55 mL/min/1.73 m^2 were randomly assigned to a usual- or a low-protein diet (1.3 or 0.58 g/kg/day) and to a usual- or a low-blood-pressure

group (mean arterial pressure, 107 or 92 mmHg) and followed for a mean of 2.2 years. In the other part, 255 patients with glomerular filtration rates of 13–24 mL/min/1.73 m^2 were randomly assigned to a low- or a very low-protein diet and similar to the first study to a usual- or a low-blood-pressure group. The low-blood-pressure group was found to have a slower decline in the glomerular filtration rate in patients who had more pronounced proteinuria at baseline (urinary protein >3 g/day), suggesting that there may be a synergistic effect between blood pressure and proteinuria in the progression of renal disease. In the low-blood-pressure group, the glomerular filtration rate declined on average by 2.8 mL/min/year in the first study (patients with GFR of 25–55 mL/min) and 3.7 mL/min/year in the second study (patients with GFR of 13–24 mL/min). If one follows the commonly accepted decline in GFR of 1 mL/min/year just from aging, then the decline in GFR in these patients with advanced kidney dysfunction seems modest. The GFR in the first group of patients averaged 38.6 mL/min at the start of the study. Considering the likely universal existence of hyperfiltration, this GFR translates into about 80–90 % renal ablation (assuming a normal GFR of 120 mL/min and a hyperfiltration quotient of about 200 %) (see Table 1). Despite this high degree of hyperfiltration and at times the continued presence of the original disease that led to the renal injury, the GFR declines were just slightly higher than what one would expect from aging. In the second study, the average GFR was 18.5 mL/min at the start of the study. With consideration of hyperfiltration, this would translate into ∼95 % renal ablation, and again even though the GFR declines faster, it was still only 3.7 mL/min/year. Thus, in this large well-done study, just from blood pressure control, one can truly minimize the effects of hyperfiltration injury to very low to non-existent levels.

Diabetes, and other diseases, associated with hyperfiltration injury

Since hyperfiltration and increased glomerular size are characteristic in early stages of type 1 diabetic kidneys, hyperfiltration is thought to play a role in the development of microalbuminuria and progressive diabetic nephropathy. Using iohexol clearance, Moriya et al. followed thirty early type 2 diabetic patients (type 2 diabetes duration, 12 ± 7 years) for a mean of 6.2 years after renal biopsy and found close negative correlation between GFR and the value of subsequent reduction in GFR in the following year [31]. In addition, urinary albumin excretion was shown to be a poor predictor of GFR decline at 1-year and 5-year periods, and the effect of lower GFR in having higher rates of GFR decline was independent of microalbuminuria. The author did not comment on the relationship between

glomerular filtration rate and HbA$_{1c}$, which predisposes to hyperfiltration in diabetic patients and is also a factor in rate of progression of diabetic kidney disease. In addition, the time from onset of diabetes was not considered when they analyzed their data as this may have an effect on the rate of progression.

In an earlier meta-analysis study, the odds of progression to microalbuminuria in a cohort of type 1 diabetic patients with hyperfiltration (varying GFRs between 125 and 140 mL/min/1.73 m^2 in the different studies) was 2.71 times that of patients with normofiltration at baseline [32]. The baseline GFR was 13.8 mL/min/1.73 m^2 greater in patient groups progressing to nephropathy than in those not progressing.

Amin et al. followed a cohort of 308 children with type 1 diabetes and examined their risk of development of microalbuminuria in relation to glomerular filtration rate and hemoglobin A1C [33]. This study, however, only found a major difference in albuminuria between the hyperfiltration group and the normofiltration group in patients who had hemoglobin A1C of >10 %. There were only 96 patients in the above hyperfiltration group, and it is not clear how many of those were followed to the age of 20 where the outcome difference was the greatest. In addition, it is not clear if the hyperfiltration group had an average hemoglobin A1C that was higher than the normofiltration group (although both were >10 %). Despite the limitations, these two studies did find hyperfiltration to be injurious in diabetic patients.

Using Cystatin C assay to estimate GFR, Ficociello et al. demonstrated no effect of hyperfiltration, whether at baseline or subsequent to disease onset, on the development of microalbuminuria in a large prospective cohort with type 1 diabetes after 15 years of follow-up [34]. There were 426 patients on this study. Confounding and effect modification due to common risk factors were evaluated in the relation between hyperfiltration and microalbuminuria and were found to be insignificant. As the author pointed out, several other studies in disagreement failed to control for confounders such as hemoglobin A1C, which again is known to be associated with increased GFR. These findings are supported by a more recent study of 2318 adults with type 1 diabetes in which Thomas et al. found no significant difference between eGFR in the diabetic study group and that expected in general Finnish population using creatinine or cystatin-based clearance formula [35]. Rather, the risk of microalbuminuria was significantly reduced in individuals with an MDRD-estimated GFR of >130 mL/min/1.73 m^2. Glycemic control, or HbA1c was found to be associated with an increased incidence of microalbuminuria, independent of eGFR. Many of the earlier studies fail to separate the effects of hyperfiltration and glycemic control. Thus the more recent, much larger studies have not

confirmed the older studies which showed an injurious effect of hyperfiltration in diabetic patients.

Obviously, there are other conditions which hyperfiltration has been classically thought to play a major role in their pathogenesis including obesity and the rare disease of oligomeganephronia. We believe with obesity induced hyperfiltration, larger well-done studies need to be done to confirm and separate the effects of hyperfiltration from other coexisting condition which may cause renal injury. Oligomeganephronia is a rare disease and the role of hyperfiltration in causing injury is much harder to discern.

Conclusion

In summary, first, it seems hyperfiltration universally happens with any significant renal ablation (50 % or more nephrectomy) in most if not all species including humans. It is our belief, however, based on data from kidney donors, nephrectomy patients, analyzing rate of chronic kidney disease progression in patients with chronic kidney disease and patients with diabetes that the hyperfiltration does not cause significant kidney injury in the great majority of patients. Glomerular hypertension may lead to renal injury but manifests as functional changes in GFR after many years if not decades later in most humans. If the inciting factors causing kidney injury are removed, renal function stabilizes in majority of patients no matter how low is the starting GFR. In conclusion, we believe (no matter how poor the renal function happens to be) in routine patient care we should not treat patients as if hyperfiltration injury will lead to end-stage kidney disease in any case. Rather we should be of the opinion that if we stop the insulting agent and control the blood pressure, we will be able to retard the progression of kidney injury no matter how bad the kidney function is at the beginning. Of course in a well-done large study looking at a public health standpoint, one may find hyperfiltration to be minimally injurious to kidney function but that does not generalize to individual patient care.

Compliance with ethical standards

References

1. Chanutin A, Ferris EB. Experimental renal insufficiency produced by partial nephrectomy. Arch Intern Med. 1932;49(5):767–87.

2. Shimamura T, Morrison AB. A progressive glomerulosclerosis occurring in partial five–sixths nephrectomized rats. Am J Pathol. 1975;79(1):95–106.

3. Hullstrom M. Development of structural kidney damage in spontaneously hypertensive rats. J Hypertens. 2012;30:1087–91.

4. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol. 1981;241(1):F85–93.

5. Olson JL, Hostetter TH, Rennke HG, Brenner BM, Venkatachalam MA. Altered glomerular permselectivity and progressive sclerosis following extreme ablation of renal mass. Kidney Int. 1982;22(2):112–26.

6. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J Clin Invest. 1986;77(6):1993–2000.

7. Griffin KA, Picken M, Bidani AK. Method of renal mass reduction is a critical modulator of subsequent hypertension and glomerular injury. J Am Soc Nephrol. 1994;4(12):2023–31.

8. Griffin KA, Picken MM, Churchill M, Churchill P, Bidani AK. Functional and structural correlates of glomerulosclerosis after renal mass reduction in the rat. J Am Soc Nephrol. 2000;11(3):497–506.

9. Yoshida Y, Fogo A, Ichikawa I. Glomerular hemodynamic changes vs hypertrophy in experimental glomerular sclerosis. Kidney Int. 1989;35:654–60.

10. Bradford JR. The results following partial nephrectomy and the influence of the kidney on metabolism. J Physiol. 1899;23(6):415–96.

11. Bainbridge FA, Beddard AP. The relation of the kidneys to metabolism. Proc R Soc. 1907;79B:75–83.

12. Abdi R, Sandroni S, Tolouian R. The inception and formation of the theory of hyperfiltration through the ages. Iran J Kidney Dis. 2012;6(2):94–7.

13. Hostetter TH. Hyperfiltration and glomerulosclerosis. Seminol Nephrol. 2003;23(2):194–9.

14. Vincenti F, Amend WJ, Kaysen G, Feduska N, Birnbaum J, Duca R, et al. Long-term renal function in kidney donors. Sustained compensatory hyperfiltration with no adverse effects. Transplantation. 1983;36(6):626–9.

15. Krohn AG, Ogden DA, Holmes JH. Renal function in 29 healthy adults before and after nephrectomy. JAMA. 1966;196(4):322–4.

16. Flanigan WJ, Burns RO, Takacs FJ, Merrill JP. Serial studies of glomerular filtration rate and renal plasma flow in kidney transplant donors, identical twins, and allograft recipients. Am J Surg. 1968;116(5):788–94.

17. Lam NN, Lentine KL, Levey AS, Kasiske BL, Garg AX. Long-term medical risks to the living kidney donor. Nat Rev Nephrol. 2015;11(7):411–9.

18. Mjøen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Øyen O, et al. Long-term risks for kidney donors. Kidney Int. 2014;86(1):162–7.

19. Muzaale AD, Massie AB, Wang M-C, Montgomery RA, McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. JAMA. 2014;311(6):579–86.

20. Grams ME, Chow EKH, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis. 2013;62(2):245–52.

21. Sanna-Cherchi S, Ravani P, Corbani V, Parodi S, Haupt R, Piaggio G, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. Kidney Int. 2009;76:528–33.

22. Westland R, Schreuder MF, Bokenkamp A, Spreeuwenberg MD, Van Wijk JAE. Renal injury in children with a solitary

functioning kidney—the KIMINO study. Nephrol Dial Transplant. 2011;26:1533–41.

23. Mavinkurve-Groothuis AMC, Van de Kracht F, Westland R, Van Wijk JAE, Loonen JJ, Schreuder MF. Long-term follow-up of blood pressure and glomerular filtration rate in patients with a solitary functioning kidney: a comparison between Wilms tumor survivors and nephrectomy for other reasons. Pediatr Nephrol. 2016;31:435–41.

24. Mitch WE, Walser M, Buffington GA, Lemann J. A simple method of estimating progression of chronic renal failure. Lancet. 1976;2(7999):1326–8.

25. Heaf JG, Mortensen LS. Uraemia progression in chronic kidney disease stages 3–5 is not constant. Nephron Clin Pract. 2011;118(4):c367–74.

26. Rutsky EA, Dubovsky EV, Kirk KA. Long-term follow-up of a human subject with a remnant kidney. Am J Kidney Dis. 1991;18(4):509–13.

27. Foster MH, Sant GR, Donohoe JF, Harrington JT. Prolonged survival with a remnant kidney. Am J Kidney Dis. 1991;17(3):261–5.

28. Novick AC, Gephardt G, Guz B, Steinmuller D, Tubbs RR. Long-term follow-up after partial removal of a solitary kidney. N Engl J Med. 1991;10325(15):1058–62.

29. Lee HC, Mitchell HC, Van Dreal P, Pettinger WA. Hyperfiltration and conservation of renal function in hypertensive nephrosclerosis patients. Am J Kidney Dis. 1993;21(Suppl 1):68–74.

30. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of diet in Renal Disease Study Group. N Engl J Med. 1994;330(13):877–84.

31. Moriya T, Tsuchiya A, Okizaki S-I, Hayashi A, Tanaka K, Shichiri M. Glomerular hyperfiltration and increased glomerular filtration surface are associated with renal function decline in normo- and microalbuminuric type 2 diabetes. Kidney Int. 2012;81(5):486–93.

32. Magee GM, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia. 2009;52(4):691–7.

33. Amin R, Turner C, van Aken S, Bahu TK, Watts A, Lindsell DRM, et al. The relationship between microalbuminuria and glomerular filtration rate in young type 1 diabetic subjects: the Oxford Regional Prospective Study. Kidney Int. 2005;68(4):1740–9.

34. Ficociello LH, Perkins BA, Roshan B, Weinberg JM, Aschengrau A, Warram JH, et al. Renal hyperfiltration and the development of microalbuminuria in type 1 diabetes. Diabetes Care. 2009;32(5):889–93.

35. Thomas MC, Moran JL, Harjutsalo V, Thorn L, Wadén J, Saraheimo M, et al. Hyperfiltration in type 1 diabetes: does it exist and does it matter for nephropathy? Diabetologia. 2012;55(5):1505–13.