Kidney Hyperfiltration After Nephrectomy: A Mechanism to Restore Kidney Function in Living Donors

Maruhum Bonar H. Marbun, Endang Susalit

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Maruhum Bonar H. Marbun, MD., PhD. Division of Nephrology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: mbhmarbun@gmail.com.

ABSTRAK

Transplantasi ginjal donor hidup (LDKT) adalah pengobatan pilihan untuk pasien dengan penyakit ginjal tahap akhir (ESRD). Hingga saat ini, penelitian yang melaporkan dampak nefrektomi pada donor ginjal yang masih hidup terhadap fungsi ginjal mereka di masa depan masih terbatas. Sebagian besar donor hidup menjalani pemulihan fungsi ginjal setelah nefrektomi karena kemampuan ginjal yang tersisa untuk mengkompensasi kehilangan nefron melalui hiperfiltrasi adaptif. Namun, hiperfiltrasi dapat gagal dan menjadi maladaptif, menyebabkan penurunan fungsi ginjal pendonor dan meningkatkan risiko penyakit ginjal kronis (PGK) dalam jangka panjang. Hiperfiltrasi disebabkan oleh peningkatan aliran darah ginjal dan hipertrofi glomerulus. Kedua kondisi tersebut diatur oleh berbagai faktor. Hiperfiltrasi adaptif pada fase awal setelah nefrektomi mungkin memainkan peran penting dalam menentukan fungsi ginjal jangka panjang, namun faktor yang mempengaruhi proses tersebut masih belum jelas. Hiperfiltrasi juga dapat dipengaruhi oleh karakteristik donor seperti usia, indeks massa tubuh (IMT), keluarga yang berhubungan dengan penerima, kekakuan arteri dan tekanan intrabdominal intraoperatif. Diperlukan studi lebih lanjut untuk memahami mekanisme hiperfiltrasi agar pusat transplantasi ginjal dapat mengantisipasi kegagalannya dan efek merugikan dari nefrektomi di masa mendatang.

Kata kunci: *hiperfiltrasi, fungsi ginjal, transplantasi ginjal, donor hidup, nefrektomi.*

ABSTRACT

Living donor kidney transplantation (LDKT) is the treatment of choice for patients with end stage renal disease (ESRD). Up to now, the studies reporting the impact of nephrectomy in living kidney donors to their future kidney function were limited. Most living donors undergo recovery of kidney function after nephrectomy owing to remnant kidneys' capability to compensate nephron loss through adaptive hyperfiltration. However, hyperfiltration may fail and turn out to be maladaptive, causing deterioration of donors' kidney function and increasing risk of chronic kidney disease (CKD) in long term. Hyperfiltration is caused by increased in kidney blood flow and glomerular hypertrophy. Both conditions are regulated by various factors. The adaptive hyperfiltration in the early phase after nephrectomy may play important role in determining long term kidney function, but factors affecting the process are still unclear. Hyperfiltration may also be influenced by donors' characteristics such as age, body mass index (BMI), family related to the recipient, arterial stiffness and intraoperative intrabdominal pressure. Further study to understand the mechanism of hyperfiltration is needed so that kidney transplant centers could anticipate its failure and the detrimental effects of nephrectomy in the future.

Keywords: *hyperfiltration, kidney function, kidney transplantation, living donor, nephrectomy.*

INTRODUCTION

Living donor kidney transplantation (LDKT) is the treatment of choice for patients with end stage renal disease (ESRD). Compared to dialysis, LDKT is associated with lower mortality and better quality of life.[1,2] While there are concerns regarding long-term risks to donors, living kidney donation is generally safe. Moreover, most studies have reported that there is no increased risk for ESRD in donors compared to general population. It may occur owing to the capability of remnant kidney to compensate kidney loss through an adaptive process called hyperfiltration.[3] Hyperfiltration allows donors' post-nephrectomy glomerular filtration rate (GFR) to increase up to 60-70% of baseline value despite 50% nephrons loss due to the procedure.[1]

The exact mechanism by which hyperfiltration occurs is not fully understood; however, it is widely suspected that hyperfiltration is caused by an increase in kidney blood flow and glomerular hypertrophy.[4] Increase in kidney blood flow is a physiologic hemodynamic response to maintain homeostasis, which is regulated by various mediators.[5] Glomerular hypertrophy increases filtration surface area, which in turn improves GFR. Post-nephrectomy glomerular hypertrophy is stimulated by various growth factors, including insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF).[6]

Hyperfiltration, however, is not always able to restore kidney function and protect donors from chronic kidney disease (CKD). Studies have reported deterioration of GFR to <60 ml/min/1.73 m^2 in 40-55% donors, six months after nephrectomy.[1,7] This may result from impairment in either blood flow or hypertrophy. Lower post-nephrectomy GFR is associated with older age, obesity, family history of CKD and arterial stiffness.[8-11]

It is important to understand the mechanism of hyperfiltration so that all kidney transplant centers could anticipate its failure and the detrimental effects of nephrectomy.

ADAPTIVE AND MALADAPTIVE HYPERFILTRATION

Hyperfiltration occurs after nephrectomy as remnant kidney attempts to maintain kidney function in spite of nephron loss. Hyperfiltration is usually an adaptive process aiming to make amends for declining filtration rate without causing any harmful effects. Previous studies have reported that adaptive hyperfiltration is influenced predominantly by increase in kidney blood flow and glomerular hypertrophy, rather than by increase in glomerular capillary pressure.[4]

Nevertheless, hyperfiltration could also bring about detrimental effects. While inadequate hyperfiltration would lead to insufficient kidney function, excessive hyperfiltration may also lead to failure in maintaining kidney function. Excessive hyperfiltration forces kidney to work more vigorously as well as causes podocyte damage and proteinuria.[5] Although excessive hyperfiltration tend to occur after a more aggressive procedure such as 5/6 nephrectomy, it is possible that similar process takes place after unilateral nephrectomy causing reduction of GFR in the long term.[12] This circumstance, in which hyperfiltration causes more harm rather than benefits, is termed maladaptive hyperfiltration.

INCREASED IN KIDNEY BLOOD FLOW

Increased in kidney blood flow is mediated by regulation of vascular pressure and resistance. Various mediators are involved in the process including nitric oxide (NO) being one of the most essential. NO is released by macula densa causes vascular relaxation through series of reaction involving guanylate cyclase and cyclic guanosine monophosphate (cGMP). The modulation of tubuloglomerular feedback starts immediately after nephrectomy, mostly during the first two days.[13] Accordingly, resistive index (RI), a parameter of kidney blood flow, increases significantly two days after nephrectomy.

Increased in kidney blood flow improves kidney oxygen supply, preventing ischemic-reperfusion injury in spite of nephrectomy-related disruption of perfusion. When kidney blood flow does not increase adequately after nephrectomy, inadequate oxygen supply forces kidney cells to carry out anaerobic metabolism. Anaerobic metabolism produces a lesser amount of adenosine triphosphate (ATP) and accumulation of lactic acid. This may alter

stability of lysosome membrane, causing leakage of hydrolase, which damages cell structure. Impaired Na/K/ATPase pump allows more sodium to enter the cell, leading to cellular edema and hydrolysis.[14]

Kidney blood flow stabilizes one week after nephrectomy, which is possibly associated with decreased kidney response to NO after seven days.[13] Accordingly, RI returns to baseline value. Such decline of RI is mainly observed in smaller, more distal vessels such as arcuate arteries. Smaller arteries may provide better portrayal of changes occurring in glomerular as they are located closely. Decline of RI throughout this period appears to be an essential part of adaptive hyperfiltration as donors with RI remaining elevated have lower GFR on the following days.

Excessive increase in kidney blood flow produces high pressure on capillary wall. Podocyte injury is caused by transmitted shear stress.[5] Structural damage of podocyte leads to loss of negative charge needed to prevent albumin passing through filtration slit. Albuminuria increases kidney workload and may cause kidney function decline in the long term.

GLOMERULAR HYPERTROPHY

The process of glomerular hypertrophy begins as early as four days after nephrectomy. Glomerular hypertrophy is induced by various growth factors including VEGF, insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF). IGF-1 is known to stimulate release of VEGF. VEGF promotes proliferation of glomerular endothelial cells, which expands filtration surface area and hence, increasing GFR.[6]

VEGF is secreted by podocytes and tubular epithelial cells to primary urine. Before acting on its receptors on endothelial cells, VEGF need to undergo back-filtration across glomerular capillary wall by diffusion and electrokinetic model.[12] Endothelial glycocalyx layer, including heparan sulfate proteoglycan, provides assistance to the process.[15] VEGF then lodges capillary lumen, increasing capillary pressure and hence, further promoting hyperfiltration.[16]

It is important to note that the surge of VEGF beyond a certain level is possibly harmful. Excessive proliferation of glomerulus widens podocyte diaphragm slit and opens fenestrae, causing albuminuria. Prolonged albuminuria injures tubular cells, lowering kidney function in the long term.[16]

ISCHEMIC-REPERFUSION INJURY

Nephrectomy may cause ischemic-reperfusion injury, which would reduce kidney function in the long term. Hyperfiltration may paradoxically cause tissue hypoxia as it increases kidney oxygen demand. Toll-like receptor (TLR4) is a part of innate immunity involved in the pathophysiology of ischemic-reperfusion injury. When ischemic-reperfusion injury occurs, tubular epithelial cells release TLR ligands called High Motility Group Box 1 (HMGB-1). TLR4 would bind with HMGB-1 and induces Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells (NF-kB). NF-kB would in turn stimulates recruitment of inflammatory cells and release proinflammatory cytokines and chemokines, including Tumor Necrosis Factor-A (TNF-a). TNF-a would later activate E-selectin, a glycoprotein expressed on the surface of endothelial cells.[17]

E-selectin mediates recruitment of polymorphonuclears (PMN) from the circulation. When activated by proinflammatory stimulus, PMN releases reactive oxygen species (ROS) through a specific process termed respiratory burst, mediated by NADPH oxidase. ROS damages glomerular filtration barrier by disrupting podocyte diaphragm slit and effacing foot processes. This structural disruption of podocytes would lead to albuminuria. ROS also washes away glycocalyx, a protective layer on the surface of endothelial glomerular cells. E-selectin also causes PMN to undergo degranulation and release lysozymes and Neutrophil Gelatinase-associated Lipocalin (NGAL).[18]

AGE

Many studies of the general population have reported the association between aging and kidney function. Older donors are believed to be at higher risk of CKD and slower recovery after nephrectomy. Various pathologic conditions could develop as someone ages, as well as normal physiologic changes including decreased

kidney responsiveness to vasodilators and vasoconstrictors. It may alter remnant kidney's ability to increase blood flow—an essential factor of adaptive hyperfiltration. Lower compliance of kidney vessels also impedes glomerular hypertrophy rendering inadequate hyperfiltration.[11] Age-related glomerulosclerosis reduces number of functional nephrons and further reducing GFR.[19] Despite evidence of age-related decline in kidney function, Toyoda et al reported no significant difference of post-nephrectomy GFR between older and younger donors. Intense monitoring may aid on preventing deterioration of kidney function in older donors after nephrectomy.[20]

BODY MASS INDEX (BMI)

BMI is widely known as a risk factor for several diseases including CKD. Aside from its association with hypertension and diabetes mellitus—two common etiologies of CKD, obesity itself causes several functional changes of kidney collectively termed obesity-related glomerulopathy. It is characterized by hyperfiltration and increased kidney blood flow to accommodate higher metabolic demand. Obese individuals are in low-grade chronic inflammatory state that renders them vulnerable to kidney damages. This inflammatory process involves adipokines such as leptin, adiponectin and also macrophages infiltration. Hormonal activities stimulate activation of proinflammatory cytokines. Obesity is also associated with an increase of oxidative stress and endothelial dysfunction.[21,22]

Nephrectomy aggravates these preexisting conditions, forcing kidney to work excessively and further impairing its function.

FAMILY HISTORY OF CKD

Previous studies of general population have reported that individuals with family history of CKD are at higher risk to acquire the same condition. Skrunes et al have reported that the relative risk of ESRD in individuals with a first-degree relative with ESRD is 7.2. When ESRD caused by hereditary etiologies is excluded, the relative risk is 3.7.23 In donor population, several studies have reported similar results. Donors with family history of CKD show lower GFR after nephrectomy.[24] Family history of CKD is associated with low nephron endowment at birth, a known risk factor to CKD.[25]

Nevertheless, association between family history and risk of CKD should not be attributed only to genetic factor. Environmental factor must also be considered as family members usually live in the same household; therefore, exposures to factors causing CKD could affect all family members.[23]

ARTERIAL STIFFNESS

Arterial stiffness is marked by elevated pulse wave velocity (PWV). In donor population, higher PWV is associated with lower hyperfiltration after nephrectomy.[9]

Contraction of the left ventricle during systole pushes blood to the arterial system in a pulsatile manner. The pulsatile waves are propagated through the arterial system from central to peripheral arteries. When this wave encounters disjunction along the arterial tree, it partly reflects backward to the aorta. Stiffer arteries propagate this backward wave more quickly leading to increased vascular pressure during systole.[26]

Normal arteries are capable of changing pulsatile flow from intermittent left ventricle ejection into a continuous flow needed to perfuse tissues and organs; therefore, reducing pressure transmitted to distal vascular walls. When arteries become stiff as a consequence of aging or other conditions, they lost this ability, causing vascular walls to receive higher pressure. Kidney microvasculature is particularly susceptible to pressure-related damage. Kidney microcirculation is characterized by low resistance and low wave reflections, rendering higher pulsatile energy transmission to the glomerulus and ultimately vascular damage. Myogenic properties of the afferent arteriole and tubule-glomerular feedback mechanism allow autoregulation of kidney blood flow despite increased transmission of pulsatile pressure to the glomerulus. This protective mechanism, however, may fail and it leads to reduction of kidney function.[26]

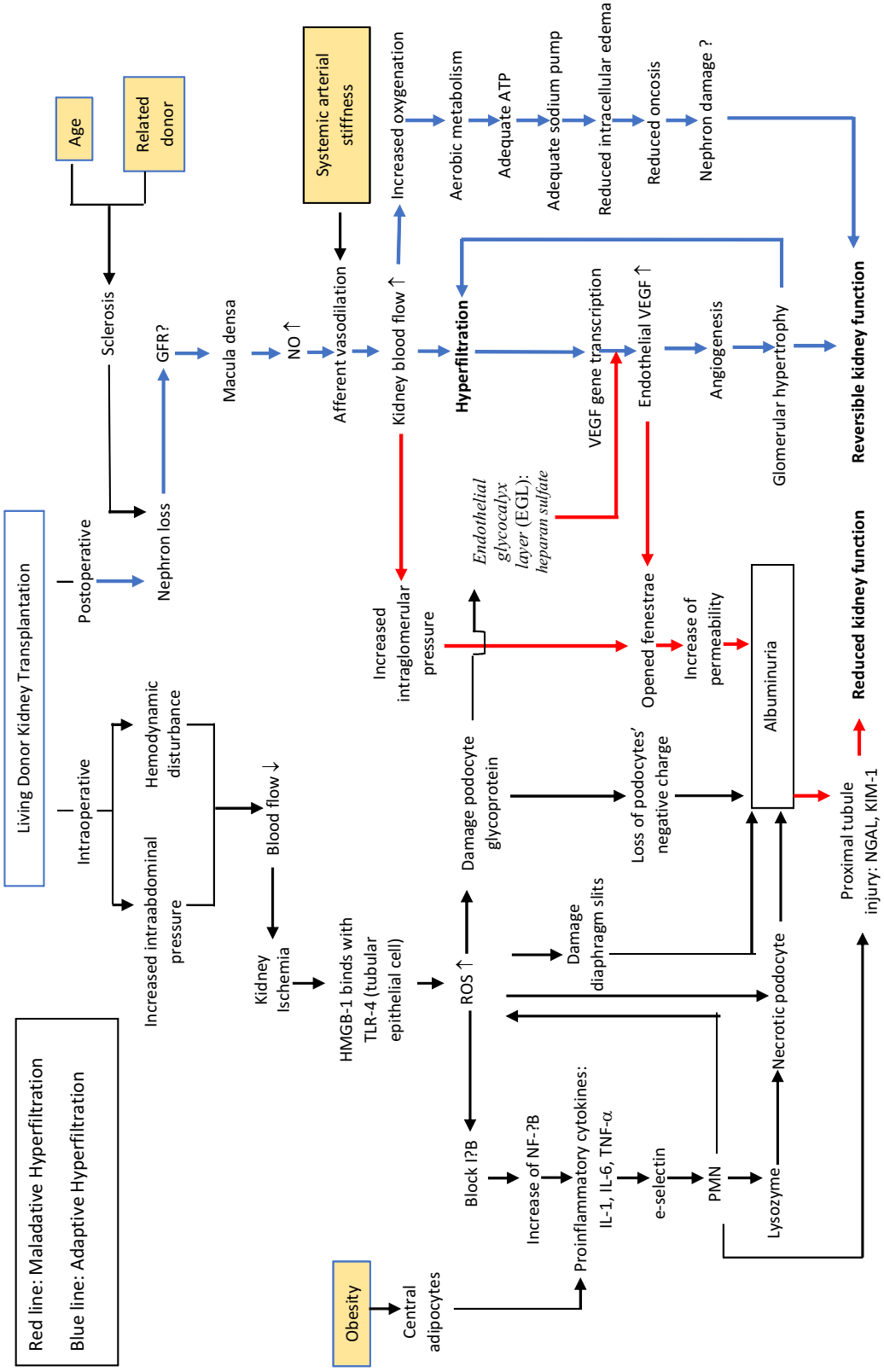

Figure 1. Scheme that illustrates factors related to kidney function after nephrectomy.

INCREASED INTRAOPERATIVE INTRAABDOMINAL PRESSURE

Laparoscopic nephrectomy may increase intraoperative intraabdominal pressure by causing pneumoperitoneum. Increased intraabdominal pressure surpassing 20 mmHg may lead to circulation problem. Kidney is greatly affected elevation of intraabdominal pressure as it reduces kidney blood flow. High pressure in the abdominal cavity may also directly compress kidney parenchyma, which causes ischemia and later injury. Cranially-displaced diaphragm compresses the heart that may lead to reduced cardiac output, which in turn cause decrease in kidney blood flow.[27,28]

CONCLUSION

After nephrectomy, living donors undergo hyperfiltration to compensate for nephron loss. Mechanisms of adaptive hyperfiltration involve an increase in kidney blood flow and glomerular hypertrophy. Donors' characteristics such as age, BMI, family history of CKD, arterial stiffness and intraoperative intrabdominal pressure may influence kidney function after nephrectomy. Factors affecting restoration of kidney function in the early phase after nephrectomy is still unclear. The mechanism related to kidney function after nephrectomy of living donor is illustrated in scheme below.

REFERENCES

1. Choi K, Yang S, Joo D, et al., editors. Clinical assessment of renal function stabilization after living donor nephrectomy. Transplantation proceedings. Elsevier; 2012.
2. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. 2011;11(10):2093-109.
3. Mueller TF, Luyckx VAJJotASoN. The natural history of residual renal function in transplant donors. 2012;23(9):1462-6.
4. Lenihan CR, Busque S, Derby G, Blouch K, Myers BD, Tan JC. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. J Clin Invest. 2015;125(3):1311-8.
5. Srivastava T, Celsi GE, Sharma M, et al. Fluid flow shear stress over podocytes is increased in the solitary kidney. 2014;29(1):65-72.
6. Chen Z, Fang J, Li G, et al., editors. Compensatory changes in the retained kidney after nephrectomy in a living related donor. Transplantation proceedings. Elsevier; 2012.
7. Kwon H, Kim D, Jang H, et al., editors. Predictive factors of renal adaptation after nephrectomy in kidney donors. Transplantation proceedings. Elsevier; 2017.
8. Muzaale AD, Massie AB, Wang M-C, et al. Risk of end-stage renal disease following live kidney donation. 2014;311(6):579-86.
9. Fesler P, Mourad G, Du Cailar G, Ribstein J, Mimran AJAJoP-RP. Arterial stiffness: an independent determinant of adaptive glomerular hyperfiltration after kidney donation. 2015;308(6):F567-F71.
10. Nogueira JM, Weir MR, Jacobs S, Breault D, Klassen D, Evans DA, et al. A study of renal outcomes in obese living kidney donors. 2010;90(9):993-9.
11. Jeon HG, Lee SR, Joo DJ, Oh YT, Kim MS, Kim YS, et al. Predictors of kidney volume change and delayed kidney function recovery after donor nephrectomy. 2010;184(3):1057-63.
12. Kuppe C, Rohlfs W, Grepl M, Schulte K, Veron D, Elger M, et al. Inverse correlation between vascular endothelial growth factor back-filtration and capillary filtration pressures. 2018;33(9):1514-25.
13. Sigmon DH, Gonzalez-Feldman E, Cavasin MA, D'Anna LP, Beierwaltes WHJJotASoN. Role of nitric oxide in the renal hemodynamic response to unilateral nephrectomy. 2004;15(6):1413-20.
14. Chatauret N, Badet L, Barrou B, Hauet TJPeu. Ischemia-reperfusion: From cell biology to acute kidney injury. 2014;24:S4-S12.
15. Gengrinovitch S, Berman B, David G, Witte L, Neufeld G, Ron DJJoBC. Glypican-1 is a VEGF165 binding proteoglycan that acts as an extracellular chaperone for VEGF165. 1999;274(16):10816-22.
16. Schrijvers BF, Flyvbjerg A, Tilton RG, Rasch R, Lameire NH, De Vriese ASJNEn. Pathophysiological role of vascular endothelial growth factor in the remnant kidney. 2005;101(1):e9-e15.
17. Wu H, Chen G, Wyburn KR, Yin J, Bertolino P, Eris JM, et al. TLR4 activation mediates kidney ischemia/reperfusion injury. 2007;117(10):2847-59.
18. Ma Y, Yabluchanskiy A, Lindsey MLJF, repair t. Neutrophil roles in left ventricular remodeling following myocardial infarction. 2013;6(1):11.
19. Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, et al. Single-nephron glomerular filtration rate in healthy adults. 2017;376(24):2349-57.
20. Toyoda M, Yamanaga S, Kawabata C, et al., editors. Long-term safety of living kidney donors aged 60 and older. Transplantation proceedings. Elsevier; 2014.
21. Suneja M, Kumar ABJJocc. Obesity and perioperative acute kidney injury: a focused review. 2014;29(4):694. e1-e6.
22. Mascali A, Franzese O, Nistico S, et al. Obesity and kidney disease: Beyond the hyperfiltration. London, England: SAGE Publications; 2016.
23. Skrunes R, Svarstad E, Reisæter AV, Vikse

BEJCJotASoN. Familial clustering of ESRD in the Norwegian population. 2014;9(10):1692-700.
24. Mjøen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. 2014;86(1):162-7.
25. Elsherbiny HE, Alexander MP, Kremers WK, et al. Nephron hypertrophy and glomerulosclerosis and their association with kidney function and risk factors among living kidney donors. 2014;9(11):1892-902.
26. I Georgianos P, A Sarafidis P, N Lasaridis AJCvp. Arterial stiffness: a novel cardiovascular risk factor in kidney disease patients. 2015;13(2):229-38.
27. Armaly Z, Abassi ZJAiN. Deleterious effects of increased intra-abdominal pressure on kidney function. 2014;2014.
28. Cheatham MLJSjot, resuscitation, medicine e. Abdominal compartment syndrome: pathophysiology and definitions. 2009;17(1):10.