CHAPTER 221

Environment, Smoking, Obesity, and the Kidney

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OBJECTIVES

This chapter will:
1. Review the effects of environment injury, smoking, and obesity in the critical ill.
2. Unravel the main pathophysiologic mechanisms of these effects.
3. Suggest preventive and therapeutic measures.

ENVIRONMENT

The kidney is especially vulnerable to toxic injury because it receives about one quarter of the cardiac output and it transports and concentrates potentially toxic compounds within its parenchyma. The main mechanisms of nephrotoxicity are vasoconstriction, altered intraglomerular hemodynamics, tubular cell toxicity, interstitial nephritis, crystal deposition, thrombotic microangiopathy, and osmotic nephrosis. Here we briefly review the role of some environmental nephrotoxins potentially responsible for causing acute kidney injury (AKI).

Environmental Nephrotoxins

The most common causes of poisoning AKI are chemicals, plants, and snake envenomation, especially in developing countries.[1] For heavy metals, please see Chapter 222.

Nephrotoxins may be pesticides, mainly paraquat and glyphosate surfactant herbicide, other chemicals (paraphenylene-diamine dye, potassium permanganate, and oxalic acid) and toxic plants as well as snake envenomation (Russell's viper, hump-nosed pit viper, saw-scaled vipers, green pit viper, sea snakes, and Bothrops and Crotalus species). Many different pathophysiologic mechanisms overlap to generate renal injury after ischemia-reperfusion injury, although pesticides and natural toxins have a very diverse range of dose-dependent mechanisms leading to AKI.

AKI following paraquat intoxication is attributed mainly to increase reactive oxygen species (ROS) generation and inflammation, whereas glyphosate surfactant causes adenosine triphosphate (ATP) depletion via uncoupling of oxidative phosphorylation, cytochrome C activation, and macromolecular oxidation.[2]

Exposure to organic solvents has been suggested to cause or exacerbate renal disease.[3] Cellular toxicity appears to derive largely from metabolic activation within cells of free radical toxic metabolites with initiation of lipid peroxidation reactions causing deleterious effect on cellular membrane structure and function. Moreover, nephrotoxins themselves may become covalently bound to cellular components, ultimately leading to nephron damage. However, methodologic concerns regarding previous studies preclude firm conclusions. The results from a recent nationwide population-based study do not support the hypothesis of an adverse effect of organic solvents on renal failure development, although detrimental effects from subclasses of solvents on specific renal diseases cannot be ruled out.[4]

Mycotoxins such as ochratoxin A, aflatoxin B, and the immunosuppressive agent cyclosporine may be nephrotoxic, and clinical syndromes have been documented.[5] Ochratoxin A is a ubiquitous nephrotoxic and carcinogenic mycotoxin considered to be involved in the cause of Balkan endemic nephropathy.[6] The occurrence of this human fatal disease that appears in regions of Bosnia, Herzegovina, Bulgaria, Croatia, Rumania, Serbia, and Montenegro correlates with very high incidence of otherwise rare urothelial tumors of the renal pelvis, and ureters. Although Ochratoxin A was found more frequently and/or in higher concentration in food and blood of inhabitants in regions with Balkan endemic nephropathy than in other regions, the involvement of Ochratoxin A in the development of Balkan endemic nephropathy is still open.

Acute ethylene glycol intoxication is a medical emergency that, if not diagnosed correctly and treated aggressively, will lead to serious neurologic, cardiopulmonary, and renal dysfunction, and may result in death.[7] Ethylene glycol toxicity is characterized by severe metabolic acidosis with high anion and osmolal gaps, and calcium oxalate crystals in the urine. Early recognition of ethylene glycol intoxication and rapid, aggressive use of large amounts of sodium bicarbonate, ethanol infusion, and hemodialysis may improve survival.

Conclusion

Acute renal damage by environmental nephrotoxins should require admittance to the intensive care unit (ICU). Clinicians need to be aware of this possibility because correct diagnosis and management are critical to prevent and manage renal damage.

SMOKING

Smoking Habit and the Intensive Care Unit Patient

Cigarette smoking is associated with excessive morbidity and mortality in various diseases, most prominently cardiovascular and lung diseases. It induces a variety of effects on the vascular and hormonal systems and is involved in the development of atherosclerosis, thrombogenesis, and vascular occlusion, all conditions that greatly influence the outcome of the critical ill patient admitted to the ICU. In fact, smokers experience an increased incidence of respiratory complications during anesthesia, have been shown to have increased risk of intraoperative and postoperative complications, and an increased risk of postoperative intensive care admittance.[8] Even passive smoking is associated with increased risk at operation. There is increasing evidence that it is also a risk factor for infection and wound-related complications. Long-term tobacco smoking (>50 pack-years)

carries a higher risk of postoperative admission to intensive care, and there seems to be a dose relationship between the amount of tobacco consumed and the risk of postoperative intensive care admission. Preoperative smoking cessation 6 to 8 weeks before surgery can reduce the complications risk significantly. Four weeks of abstinence from smoking seems to improve wound healing. An intensive, individual approach to smoking intervention results in a significantly better postoperative outcome. Future research should focus upon the effect of a shorter period of preoperative smoking cessation. All smokers admitted for surgery should be informed of the increased risk, recommended preoperative smoking cessation, and offered a smoking intervention program whenever possible.[9]

Smoking as a Renal Risk Factor

Despite increasing evidence, cigarette smoking has not been acknowledged sufficiently as a major renal risk factor either in the general population, either in the ICU patient.[10] Smoking habit is reported to be associated with renal damage in the general population increasing, particularly in men and in the elderly, the albumin excretion rate even in a range below the level of microalbuminuria.[11] Moreover, it is clear that smoking increases not only the risk of albuminuria/proteinuria but also that of renal functional deterioration.[11] Cigarette smoking was related to the development of renal disease in different ethnic groups such as African Americans[12] and Hispanics and for intermittent smokers.[13]

Diabetologists were the first to recognize the adverse effects of smoking on the kidney: in type 1 and in type 2 diabetes, smoking increases the risk of nephropathy development and nearly doubles the rate of progression to end-stage renal failure. In fact, in patients with diabetes smoking not only increases the risk to develop microalbuminuria[14] but also accelerates the rate of progression from microalbuminuria to manifest proteinuria,[15] and eventually to renal failure.[16]

Smoking also has been shown to increase the risk of progression to end-stage renal disease (ESRD) in patients with primary renal disease, with inflammatory and noninflammatory renal disease (i.e., IgA glomerulonephritis and polycystic kidney disease).[17,18]

Potential Mechanisms of Smoking-Related Nephrotoxicity

Several potential mechanisms of smoking-induced renal dysfunction and damage have been discussed,[10,18] but the precise nature of the nephrotoxic effect of smoking is not well understood (Box 221.1). Smoking may induce albuminuria and abnormal renal function through advanced glycation end products. It is known that advanced glycation end products are responsible for enhanced vascular permeability and that they accelerate vasculopathy of end-stage diabetic renal disease. Moreover, aqueous extracts of tobacco and cigarette smoke contain glycotoxins, highly reactive glycation products that rapidly can induce in vitro and in vivo formation of advanced glycation end products on proteins.[19] It is reasonable to expect that the advanced glycation end products formed by the reaction of glycotoxins from cigarette smoke with serum and tissue proteins will affect the systemic and renal vasculature (Box 221.2).

Insulin resistance may be another possible mechanism underlying the pathophysiologic effects of smoking-induced renal damage.[18] Several investigators have found smoking to be causally related to insulin resistance in nondiabetic persons. Insulin resistance has been known to be related to albuminuria and abnormal renal function. Both of these mechanisms—advanced glycation end products and insulin resistance—may act through endothelial dysfunction; that is, by inducing an imbalance between the contracting and relaxing substances produced by the endothelium. The plasma concentration of endothelin has been shown to be increased in smokers compared with nonsmokers, and further indirect evidence supports a disturbance of endothelin, prostacyclin, or nitric oxide release on stimulation in smokers. Interestingly, smoking by the induction of hypoxic stress may interfere with vascular endothelial growth factor (VEGF) synthesis and activity; VEGF is a potent mitogen for endothelial cells, plays a central role in the regulation of vasculogenesis and vascular permeability, and seems to be involved in diabetic complications.

Moreover, smoke also has been shown to induce structural damage to the renal tissue. The smokers had a smoking dose-dependent increase in glomerular basement membrane (GBM) width, which along with mesangial expansion and arteriolar hyalinosis, are the structural hallmarks of diabetic nephropathy.[20] Recently, Jaimes et al. demonstrated that human mesangial cells are endowed with the nicotinic receptors (nAChRs) alpha4, alpha5, alpha7, beta2, beta3, beta4, and beta5.[21] In this manner nicotine may accelerate and promote the progression of kidney disease. Moreover, smoking may be associated with podocyte injuries in patients with early diabetic nephropathy. More podocytes are excreted in the urine of smokers with microalbuminuria than nonsmokers with microalbuminuria. As a matter of fact, urinary podocytes disappeared after 3 years in 10 of the 13 patients who had stopped smoking, whereas urinary podocytes increased in all patients who continued to smoke.[22]

The nicotine-induced increase in blood pressure and heart rate via sympathetic activation and vasopressin release appears to be a major mechanism contributing to the adverse

BOX 221.1

Smoking-Related Renal Damage: Main Potential Pathomechanisms

- Increase sympathetic activity: ↑ BP and HR
- Alterations in intrarenal hemodynamics: ↓ GFR, ↓ FF, ↓ RPF, ↑ RVR
- Cellular toxic effects: ↑ oxidative stress, ↓ NO, ↑ ET-1
- Hormonal imbalance: ↑ insulin resistance, ↑ vasopressin

BP, Blood pressure; *ET-1,* endothelin-1; *FF,* filtration fraction; *GFR,* glomerular filtration rate; *HR,* heart rate; *NO,* nitric oxide; *RPF,* renal plasma flow; *RVR,* renal vascular resistance.

BOX 221.2

Smoking-Related Renal Damage: Main Potential Pathophysiologic Mechanisms

- Increase sympathetic activity: ↑ BP and HR
- Alterations in intrarenal hemodynamics: ↓ GFR, ↓ FF, ↓ RPF, ↑ RVR
- Cellular: ↑ oxidative stress, ↓ NO, ↑ ET-1
- Hormonal imbalance: ↑ insulin resistance, ↑ vasopressin

BP, Blood pressure; *ET-1,* endothelin-1; *FF,* filtration fraction; *GFR,* glomerular filtration rate; *HR,* heart rate; *NO,* nitric oxide; *RPF,* renal plasma flow; *RVR,* renal vascular resistance.

renal effects of smoking.[10] Nicotine, apart from the above cited cellular effects, directly stimulates catecholamine release from peripheral sympathetic nerve endings and the adrenal medulla. On the basis of these vasoactive effects of smoking, it has been hypothesized that repeated episodes of acute renal hypoperfusion induced by smoking may favor structural alterations of preglomerular vessels and glomerular obsolescence, thus leading to hypertrophy and hyperfiltration of remnant glomeruli,[23] which would explain the elevated glomerular filtration rate (GFR) (a predictor of GBM thickening, an early marker of kidney disease in diabetes) observed in current smokers compared with nonsmoker patients and with those who had stopped smoking.

Cigarette smoke, in addition, exerts an inhibitory effect on components of the L-arginine-nitric oxide pathway. Therefore potential effects of cigarette smoking on the availability of intracellular L-arginine may be one mechanism adversely influencing the survival of endothelial cells in the setting of oxidative stress and progressive atherosclerosis. Therefore excessive or prolonged signaling induced by cigarette smoking may contribute to pathologic fibrosis, scarring, and matrix deposition (i.e., remodeling, in a surprising variety of diseases including above all diabetic nephropathy).[24]

Whether a genetic susceptibility determines an increased renal risk in smokers is an issue that deserves further investigation. In this context, a result of the Bergamo NEphrologic DIabetes Complications Trial (BENEDICT) is noteworthy: a genetic predisposition of smokers to develop albuminuria was found in carriers of the DD-genotype of the ACE gene.[25]

Conclusion

In conclusion, smoking is clearly a risk factor for kidney involvement in the critical ill patients. Smoking cessation is an opportunity after critical illness. Smokers make up a high percentage of patients admitted to ICU, and the message to stop smoking must be given clearly to recovering patients. The recovery period provides an important opportunity for patients to quit smoking as the period of sedation and ventilation allows patients to start nicotine withdrawal. However, the clearance of smoking effects that impact renal disease, such as oxidative stress and epigenetic changes, take a long time, which is more similar to cancer than it is to CVD.[26]

OBESITY

Obesity and the Intensive Care Unit Patient

Obese critically ill patients present unique challenges: physiological changes, differences in risk of organ dysfunction and complications, drug dosing alterations, and logistical issues must be understood to provide the best possible care.[27] These clinical conditions are increasingly recognized because the prevalence of obesity in ICUs is estimated at 25%, morbid obesity (BMI > 40 kg/m^2) being 6.3%.

Critically ill obese patients are at increased risk of morbidity and mortality compared with the nonobese patients.[28,29] Obstructive airway disease, pneumonia, and sepsis are the main reasons for admission to the ICU in the morbidly obese group; they show higher rates of mortality, nursing home admission, and intensive care unit complications including sepsis, nosocomial pneumonia, acute respiratory distress syndrome, catheter infection, tracheostomy, and acute renal failure. Moreover, they have longer stays in the ICU and time on mechanical ventilation.[28,29] The care of critically ill obese patients often is complicated by the derangements in cardiovascular, respiratory, metabolic, and kidney function, all features of chronic obesity. In this regard, drug administration may be affected depending on the lipophilicity of the molecule administered; the ability to gain vascular access often is impaired because of large body habitus and should be aided with ultrasound guidance; and the fidelity of blood pressure monitoring also can be affected adversely, necessitating the use of direct intraarterial monitoring.[30] However, in recent years the outcome of obese ICU patient seems to be improved.[30]

Obesity: An Independent Risk Factor for Renal Damage

Obesity is a well-recognized risk factor for diabetes and hypertension; thus the global obesity epidemic translates into substantially heightened chronic kidney disease (CKD) risk factors worldwide. Obesity, especially abdominal obesity, not only increases the risk of hypertension but also makes hypertension more resistant to treatment. The higher blood pressures associated with overweight and obesity are probably the result of multiple factors and include activation of the sympathetic nervous and renin–angiotensin systems, increased serum leptin levels, volume expansion, and sleep apnea. Uncontrolled hypertension in obese adults certainly may accelerate loss of kidney function over time, especially when compounded by the additional CKD risks, which accompany obesity.[31]

However, aside from its link with traditional CKD risk factors, obesity may increase susceptibility to CKD via several potential mechanisms. In fact, an array of cross-sectional and longitudinal studies from diverse populations have secured the importance of higher body weight for height as a risk factor for the prevalence and progression of CKD.[32,33] This causal association has mechanisms different than that of the so-called inverse epidemiology of ESRD patients, a condition in which a paradoxic association between higher body weight for height and survival has been found,[34] a finding almost certainly explained by residual confounding by malnutrition and competing mortality risks in the years preceding ESRD. The relation between excess weight and risk of CKD and ESRD appeared to persist even after accounting for the presence or absence of baseline diabetes and hypertension. Obesity, although having the strongest association with diabetic nephropathy, also had a two- to three-fold risk elevations for all major subtypes of CKD. Analyses that were confined to strata without hypertension or diabetes revealed a threefold increased risk among patients who were overweight at age 20, whereas the twofold observed risk elevation among those who had a highest lifetime BMI of more than 35 was statistically insignificant.[35] So, obesity seems to be an important, potentially preventable, risk factor for CKD with additional pathways different from that of hypertension and type 2 diabetes.

Pathophysiologic Mechanisms of Obesity-Related Renal Damage

Obesity is an established risk factor for CKD because it is associated with an array of comorbidities and with glomerular lesions potentially related to a supranormal GFR; it has also been identified as a risk factor for acute

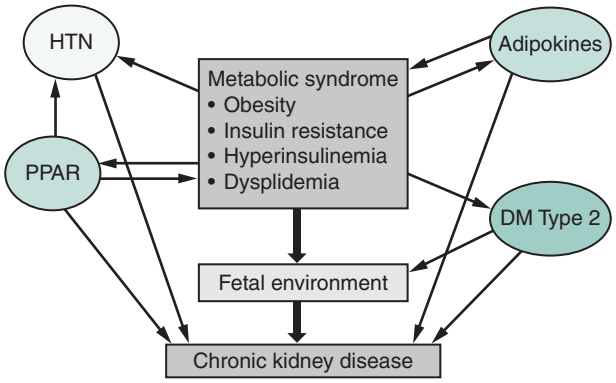

FIGURE 221.1 Obesity-related renal damage.

kidney injury (AKI) in patients suffering from trauma, acute respiratory distress syndrome (ARDS), but also in the general ICU populations.[27]

There are several molecular mechanisms that have been proposed for the obesity-related renal damage (Fig. 221.1).[36] First of all, adipose tissue is now recognized as an active endocrine organ that can affect the function of other organs and an important source of proinflammatory cytokines, chemokines, growth factors, and complement proteins called adipokines. Almost all influence the cardiovascular system; many of them influence kidney function and should be related to the outcome of the obese patient, especially the critical ill one. In this regard, leptin is the hallmark of these substances. In fact, it stimulates the activity of the sympathetic nervous system, the endocapillary cell proliferation, and mesangial collagen deposition; moreover, its renal effect has natriuretic properties and the ability to stimulate reactive oxygen species. So, it exerts a deteriorative impact on the cardiovascular system and kidneys by its significant contribution to the pathogenesis of obesity-related hypertension and nephropathy.[37] On the other hand, in the ICU patient leptin secretion is closely linked to the functions of the hypothalamic-pituitary-adrenal (HPA) axis and the immune system, both of which are crucial in influencing the course and outcome of critical illness. Leptin and interleukin-6 (IL-6) are oversecreted in acute critical illness, such as sepsis. Leptin inhibits, whereas IL-6 stimulates, the HPA axis. The negative relation between IL-6 and leptin is paramount, because high IL-6 levels are associated with poor outcome in critically ill patients, whereas plasma leptin levels are increased in survivors of acute sepsis; relatively low leptin levels may impair sympathetic system and immune functions.[38]

The leading hypothesis is that additional obesity-associated factors may increase renal risk. Adipose production of these mediators, as well as adipokines such as leptin, in response to acute illness could contribute to the obesity-AKI link. Another relevant mechanism may be related to the intraabdominal hypertension that may cause renal dysfunction from venous congestion and poor arterial perfusion leading to ischemic and congestive AKI.[27]

Another potential pathophysiologic link between obesity and renal damage may be the metabolic syndrome. The fact that central adiposity modifies the association between overweight and obesity and measures of CKD point to the potential role of the metabolic syndrome. Central adiposity frequently is accompanied not only by hypertension but also by hypertriglyceridemia, decreased levels of high-density lipoprotein (HDL) cholesterol, enhanced inflammation, and a prothrombotic state. These metabolic changes reflect a state of insulin resistance and its interaction with obesity.[37]

Evidence linking metabolic syndrome and renal disease recently has emerged. It has been speculated that early renal damage occurs in obesity-initiated metabolic syndrome.[39] Several pathophysiologic pathways have been considered, either as single or combined mechanisms: (1) adverse effects of increased body mass and excretory load, (2) obesity-induced sodium retention, (3) direct or indirect effects of hyperinsulinemia/insulin resistance, and (4) renal lipotoxicity.

Metabolic syndrome represents hyperinsulinemia, which may lead to structural renal changes.[31,38] Increased metabolic demands on the kidney also may mediate increased CKD risk in overweight and obese individuals. Weight gain increases the work of each individual nephron. Body size is correlated positively with glomerular size, GFR, and effective renal plasma flow. Increased filtration fraction in overweight and obese individuals in the presence of increased blood flow suggests the potential existence of increased glomerular capillary pressure. As an individual gains weight, single-nephron GFR must increase, and this occurs at the expense of increased capillary pressures.[39] These changes predispose the glomerular capillary wall to hemodynamic injury and glomerular hypertrophy. Thus in the setting of obesity, there are multiple stimulants of transforming growth factor beta 1 (TGF-1), including increased insulin and angiotensin II levels, increased glomerular volume, and capillary pressures. These factors interact and promote structural changes and glomerular damage. Individuals with reduced nephron mass possess a high risk for CKD in the setting of overweight and obesity. The compensatory glomerular hypertrophy among individuals with reduced nephron mass is compounded by the increased metabolic load imposed on the kidney by overweight and obesity. These individuals are also at high risk for subsequent development of other CKD risk factors, including hypertension and diabetes. However, this cascade of CKD risk factors can be avoided if these individuals with reduced nephron mass maintain an ideal body weight.

Obesity, especially morbid obesity, has been linked with focal segmental glomerulosclerosis (FSGS).[40] Obesity is unlikely to be the sole mediator of secondary FSGS, given the rarity of this disease in the general population contrasted with the high prevalence of obesity. However, within a background of genetic susceptibility and perhaps other clinical risk factors including sleep apnea and reduced nephron number, obesity could potentiate development of secondary FSGS.

Management of Kidney Disease in the Obese Patient in the Intensive Care Unit

GFR evaluation is challenging in this patient population because the estimating formulas used have limitations when used during critical illness because of the dynamic fluid, metabolic, hemodynamic, and hormonal changes.[31] Obese individuals may have glomerular hyperfiltration and higher creatinine generation caused by increases in fat and lean body mass as total body weight increases. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation may yield the best results in obese patients.[41]

The limitations of current consensus criteria for AKI should be kept in mind when interpreting studies of obese patients, because the indexing of urine output criteria to weight may misclassify obese patients as having AKI.[27]

Healthcare providers need to be aware that management and the necessary supportive care, such as renal replacement therapy requiring vascular access, may be challenging

because of the difficulties in obtaining vascular access for initiation for dialysis.[42] Compounding this challenge is the fact that the methods to precisely calculate the dialysis dose, such as continuous venovenous hemofiltration (CVVH), are not well established in this patient population. Among morbidly obese patients, dosing based on actual weight leads to an impractical, large, and possibly unsafe volume of replacement fluid. Although there is a lack of evidence, estimated lean body weight adjustments probably should be used for dose calculations.[43]

Conclusion

Obesity has clear pathophysiologic effects upon the kidneys. A thorough knowledge of the unique pathophysiologic changes that occur in this population will allow prevention and more effective treatments in the ICU setting.

Key Points

1. Environment is a possible source of acute nephrotoxic damage.
2. Smoking may induce albuminuria and abnormal renal function.
3. Obesity is an independent risk factor for chronic kidney disease and may induce kidney injury.
4. Smoking habit and obesity influence the outcome of the intensive care unit patients.

Key References

1. Mohamed F, Endre ZH, Buckley NA. Role of biomarkers of nephrotoxic acute kidney injury in deliberate poisoning and envenomation in less developed countries. *Br J Clin Pharmacol*. 2015;80(1):3-19.
2. Wimalawansa SJ. The role of ions, heavy metals, fluoride, and agrochemicals: critical evaluation of potential aetiological factors of chronic kidney disease of multifactorial origin (CKDmfo/CKDu) and recommendations for its eradication. *Environ Geochem Health*. 2016;38:639-678.

12. Hall ME, Wang W, Okhomina V, et al. Cigarette smoking and chronic kidney disease in African Americans in the Jackson Heart Study. *J Am Heart Assoc*. 2016;5(6):pii: e003280. doi:10.1161/JAHA.116.003280.
13. Franceschini N, Deng Y, Flessner MF, et al. Smoking patterns and chronic kidney disease in US Hispanics: the Hispanics Community Health Study/the Study of Latinos. *Nephrol Dial Transplant*. 2016 Jun 2. pii: gfw210;[Epub ahead of print].

27. Shashaty MG, Stapleton RD. Physiological and management implications of obesity in critical illness. *Ann Am Thorac Soc*. 2014;11(8):1286-1297.

A complete reference list can be found online at ExpertConsult.com.

References

1. Mohamed F, Endre ZH, Buckley NA. Role of biomarkers of nephrotoxic acute kidney injury in deliberate poisoning and envenomation in less developed countries. *Br J Clin Pharmacol*. 2015;80(1):3-19.
2. Wimalawansa SJ. The role of ions, heavy metals, fluoride, and agrochemicals: critical evaluation of potential aetiological factors of chronic kidney disease of multifactorial origin (CKDmfo/CKDu) and recommendations for its eradication. *Environ Geochem Health*. 2016;38:639-678.
3. Kluwe WM. The nephrotoxicity of low molecular weight halogenated alkane solvent, pesticides, and chemical intermediates. In: Hook JB, ed. *Toxicology of the Kidney*. New York: Raven Press; 1981.
4. Fored CM, Nise G, Ejerblad E, et al. Absence of association between organic solvent exposure and risk of chronic renal failure: a nationwide population-based case-control study. *J Am Soc Nephrol*. 2004;15(1):180-186.
5. Krogh P. Mycotoxic nephropathies. *Adv Vet Sci Comp Med*. 1976;20:147.
6. Fuchs R, Peraica M. Ochratoxin A in human kidney diseases. *Food Addit Contam*. 2005;22(suppl 1):53-57.
7. Cox RD, Phillips WJ. Ethylene glycol toxicity. *Mil Med*. 2004;169(8):660-663.
8. Moller AM, Maaloe R, Pedersen T. Postoperative intensive care admittance: the role of tobacco smoking. *Acta Anaesthesiol Scand*. 2001;45(3):345-348.
9. Moller A, Tonnesen H. Risk reduction: perioperative smoking intervention. *Best Pract Res Clin Anaesthesiol*. 2006;20(2): 237-248.
10. Orth SR. Smoking–A renal risk factor. *Nephron*. 2000;86:12-26.
11. Orth SR, Ritz E, Schrier RW. The renal risks of smoking. *Kidney Int*. 1997;51:1669-1677.
12. Hall ME, Wang W, Okhomina V, et al. Cigarette smoking and chronic kidney disease in African Americans in the Jackson Heart Study. *J Am Heart Assoc*. 2016;5(6):pii: e003280. doi:10.1161/JAHA.116.003280.
13. Franceschini N, Deng Y, Flessner MF, et al. Smoking patterns and chronic kidney disease in US Hispanics: the Hispanics Community Health Study/the Study of Latinos. *Nephrol Dial Transplant*. 2016 Jun 2. pii: gfw210. [Epub ahead of print].
14. Chase HP, Garg SK, Marshall G, et al. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA*. 1991;265:614-617.
15. Mühlhauser I, Sawicki P, Berger M. Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in type 1 (insulin-dependent) diabetes. *Diabetologia*. 1986;29:500-502.
16. Biesenbach G, Janko O, Zazgornik J. Similar rate of progression in the predialysis phase in type I and type II diabetes mellitus. *Nephrol Dial Transplant*. 1994;9:1097-1102.
17. Orth SR, Stockmann A, Conradt C, et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int*. 1998;54(3):926-931.
18. Pinto-Sietsma SJ, Mulder J, Janssen WM, et al. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med*. 2000;133:585-591.
19. Cerami C, Foundes H, Nicholl I, et al. Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci USA*. 1997;94:13915-13920.
20. Mauer SM. Structural-functional correlations of diabetic nephropathy. *Kidney Int*. 1994;45:612-622.
21. Jaimes E, Tian RX, Raij L. Nicotine: The link between cigarette smoking and the progression of renal injury? *Am J Physiol Heart Circ Physiol*. 2006.
22. Nakamura T, Kawagoe Y, Koide H. Effect of cigarette smoking on urinary podocyte excretion in early diabetic nephropathy. *Diabetes Care*. 2003;26:1324-1325.
23. Remuzzi G. Effect of cigarette smoking on renal function and vascular endothelium. *Contrib Nephrol*. 2000;130:45-52.
24. De Cosmo S, Lamacchia O, Rauseo A, et al. Cigarette smoking is associated with low glomerular filtration rate in male patients with type 2 diabetes. *Diabetes Care*. 2006;29(11):2467-2470.
25. Perna A, Iordache BE, Bettinaglio P, et al. DD ACE genotype and smoking cluster with high-normal albuminuria: a cross sectional analysis in 1209 normo-albuminuric type 2 diabetics enrolled in the BErgamo NEphrologic DIabetes Complications Trial (BENEDICT). *J Am Soc Nephrol*. 2001;12:154A.
26. Nagasawa Y, Kida A, Nakanisihi T. Effect of cigarette smoking cessation on CKD: is it a cancer-suppression-like effect or a CVD-suppression-like effect? *Hypertens Res*. 2016 Jun 16; doi:10.1038/hr.2016.62. [Epub ahead of print].
27. Shashaty MG, Stapleton RD. Physiological and management implications of obesity in critical illness. *Ann Am Thorac Soc*. 2014;11(8):1286-1297.
28. Yaegashi M, Jean R, Zurigat M, et al. Outcome of morbid obesity in the intensive care unit. *J Intensive Care Med*. 2005;20(3):147-154.
29. El-Solh A, Sikka P, Bozkanat E, et al. Morbid obesity in the medical ICU. *Chest*. 2001;120(6):1989-1997.
30. Joffe A, Wood K. Obesity in critical care. *Curr Opin Anaesthesiol*. 2007;20(2):113-118.
31. Kramer H. *Obesity and Chronic Kidney Disease Contrib Nephrol*. Vol. 151. 2006:1-18.
32. Iseki K, Ikemiya Y, Kinjo K, et al. Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int*. 2004;65:1870-1876.
33. Ejerblad E, Fored CM, Lindblad P, et al. Obesity and risk for chronic renal failure. *J Am Soc Nephrol*. 2006;17:1695-1702.
34. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al. Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J Kidney Dis*. 2005;46:489-500.
35. Chudek J, Adamczak M, Nieszporek T, et al. The adipose tissue as an endocrine organ - A nephrologist' perspective. *Contrib Nephrol*. 2006;151:70-90.
36. Torpy DJ, Bornstein SR, Chrousos GP. Leptin and interleukin-6 in sepsis. *Horm Metab Res*. 1998;30(12):726-729.
37. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med*. 2004;140:167-174.
38. Bagby SP. Obesity-initiated metabolic syndrome and the kidney: a recipe for chronic kidney disease? *J Am Soc Nephrol*. 2004;15:2775-2791.
39. Praga M. Obesity—A neglected culprit in renal disease. *Nephrol Dial Transplant*. 2002;17:1157-1159.
40. Praga M, Hernandez E, Morales E, et al. Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. *Nephrol Dial Transplant*. 2001;16:1790-1798.
41. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 ml/min/1.73 m^2. *Am J Kidney Dis*. 2010;56:486-495.
42. Collins J. Nutrition and care considerations in the overweight and obese population within the critical care setting. *Crit Care Nurs Clin North Am*. 2014;26(2):243-253.
43. McAtee ME. Nursing care of the critically Ill obese patient. In: El Solh AA, ed. *Critical Care Management of the Obese Patient*. Oxford, UK: Wiley-Blackwell; 2012.