Drug-Induced Nephrotoxicity: A Review

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ABSTRACT

Background: Nephrotoxicity is referred to as rapid degeneration in kidney functioning due to the toxic effects of medications. The glomerulus and proximal renal tubule are the fundamental portions of the nephron to be affected by drugs leading to nephrotoxicity. Prescribed medications like antibiotics (aminoglycoside, and vancomycin), amphotericin B, antidepressants (amitriptyline, fluoxetine), acyclovir, angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, cocaine, statins, antihistamines (Diphenhydramine), and sulfonamides can result in specific outcomes relative to nephrotoxicity, such as renal injury, inflammation, platelet aggregation, cell cytotoxicity, thrombosis, reduced renal blood flow, and crystal precipitation result in nephrotoxicity.
Objective: we aimed to review the various pathogenic mechanisms responsible for drug-induced nephrotoxicity including, altered intra-glomerular hemodynamics, tubular cell toxicity, renal inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. The review also highlights risk factors related to the patient and the drugs being prescribed. The majority of the nephrotoxicity risk factors depend on the patients' age, gender, pre-existing renal insufficiency, drug dosage, and hypersensitivity to drug toxicity.
Methods: We have searched the different databases to recruit published material mainly focusing on Pubmed, GoogleScholars, and Iraqi Virtual Science Library.
Conclusion: To sum up, the review explains the necessity of evaluating nephrotoxicity, drug dosage, and risk factors as primary preventive measures to avoid drug-induced Nephrotoxicity.

Keywords: Nephrotoxicity, renal insufficiency, antibiotics, proximal tubules.

السمية الكلوية بواسطة الادوية

المدخل: تميل المراجعة التالية إلى تقييم ظاهرة السمية الكلوية التي يسببها الدواء. تم شرح العديد من الميزات ذات الصلة بالسمية الكلوية، بما في ذلك الآليات المسببة للأمراض، وعوامل الخطر، والأدوية المرتبطة، والتدابير الوقائية المحددة، المذكورة في البحوث المنشورة. يشار إلى السمية الكلوية بالتنكس السريع في وظائف الكلى بسبب التأثيرات السامة للأدوية.
الهدف: تهدف الدراسة الى مراجعة الآليات المسببة للأمراض المختلفة المسؤولة عن تطور السمية الكلوية التي يسببها الدواء ، ديناميكا الدم داخل الكبيبة المعدلة ، وتسمم الخلايا الأنبوبية ، والتهاب الكلى ، واعتلال الكلية البلوري ، وانحلال الربيدات ، واعتلال الأوعية الدقيقة الخثاري. ومع ذلك ، فإن الكبيبة والنبيبات الكلوية القريبة هي الأجزاء الأساسية من النيفرون التي تتأثر بالأدوية التي تؤدي إلى السمية الكلوية. يمكن أن تؤدي الأدوية الموصوفة مثل المضادات الحيوية (أمينوغليكوزيد وفانكومايسين) والأمفوتريسين ب ومضادات الاكتئاب (أميتريبتيلين وفلوكستين) وأسيكلوفير ومثبطات الإنزيم المحول للأنجيوتنسين ومضادات الالتهاب غير الستيروئيدية والستاتينات ومضادات الهيستامين (ديفينهيدرامين) والسلفونواميدات إلى نتائج محددة. مثل إصابة الكلى ، الالتهاب ، تراكم الصفائح الدموية ، السمية الخلوية للخلايا ، تجلط الدم ، انخفاض تدفق الدم الكلوي ، وتساقط الكريستال يؤدي إلى السمية الكلوية. تبرز المراجعة أيضًا عوامل الخطر المتعلقة بالمريض والأدوية التي يتم وصفها. تعتمد غالبية عوامل خطر

السمية الكلوية على عمر المريض، والجنس، والقصور الكلوي الموجود مسبقًا، وجرعة الدواء، وفرط الحساسية لسمية الأدوية. أخيرًا ، تشرح المراجعة أيضًا ضرورة تقييم السمية الكلوية وجرعة الدواء وعوامل الخطر كإجراءات وقائية أولية لتجنب السمية الكلوية التي يسببها الدواء.

طرق العمل: تم البحث في قواعد البيانات المختلفة لتجنيد مواد منشورة تركز بشكل اساسي على Pubmed وGoogle scholars ومكتبة العلوم الافتراضية العراقية.

الملخص: اختصارا نشرح المراجعة ضرورة تقييم السمية الكلوية وجرعه الدواء وعوامل الخطر كإجراءات وقائية أولية لتجنب السمية الكلوية التي يسببها الدواء.

الكلمات المفتاحية: السمية الكلوية، اعتلال الكلية ، المضادات الحيوية، الانابيب الدانية.

INTRODUCTION

Medications have been playing a significant role in disease management for centuries. According to prescription drug statistics 2021, an estimated 66% of American adults take prescription medication, and 131 million individuals from the population in the United States take at least one of the prescribed medications[1]. However, their adverse effects could not be neglected entirely, as proven by modern sciences. Statistical research department in 2016 disclosed that around 4% of the adult Americans in the United States experienced severe side effects after taking a prescribed medication in the last five years (1). Although several side effects could be mild such as skin rash, allergies, infections, diarrhea, constipation, insomnia, etc. The primary focus of this review is to explore drug-nephrotoxicity, which is considered as an acute drug side effect. Al-Naimi et al. (2019) described Nephrotoxicity as a rapid degeneration in the functioning of the kidney due to the adverse or toxic effects of medications[2]. Kim and Moon (2012), mentioned that consumption of drugs are responsible for inducing and causing approximately 20% of nephrotoxicity in all cases[3]. Young children, infants, and patients suffering from specific clinical issues associated with cardiovascular diseases and renal dysfunction are more vulnerable to developing drug-induced nephrotoxicity[4]. Patients suffering from renal failure tend to have profound nephrotoxic effects, whereas the rate of nephrotoxicity increases up to 66% among elders when treated with medications[5]. The substances that are responsible for the toxicity are referred to as nephrotoxins[6]. Specific symptoms of nephrotoxicity involve malaise, vomiting, anorexia, shortness of breath, and edema[7]. Alongside decreased urine output provides a most significant sign of nephrotoxicity[8].

Etiology of nephrotoxicity

A kidney is considered an essential organ as it tends to perform several main functions in the body, such as extracellular environment regulation and homeostasis maintenance[9]. Kidneys could be considered as a determinant organ for exogenous toxicants as kidneys are responsible for detoxification and excretion of drugs and toxic substances, therefore, inefficient excretion of toxic metabolites by the kidney may lead to nephrotoxicity[3]. Pathogenic mechanisms entail various processes through which a substance or microbe can cause disease or damage the host, Shahrbaf and Assadi, (2015) mentioned several drug-associated pathogenic mechanisms that eventually lead to nephrotoxicity, such as glomerular damage, renal tubular toxicity, renal inflammation, thrombotic microangiopathy, crystal nephropathy, etc[4].

Renal Hemodynamics

Each kidney comprises almost of 1 million filtering units referred to as nephrons. The glomerulus is a portion of the nephron which is a specialized bundle of capillaries where filtration takes place[10]. The term "hemodynamics" is used to describe blood flow through an organ structures, including kidneys, in the body and, therefore, is associated with cardiovascular functionality measures, including cardiac output and arterial pressure[11]. Based on this definition, intra-glomerular hemodynamics could be illustrated as the blood pressure and flow through glomerulus capillaries (Saulnier et al., 2021)[12]. Afferent and efferent arterioles regulate the blood flow through each glomerulus. The relative vasoconstriction and vasodilation of these efferent and afferent arterioles determine the pressure within each glomerulus. This is known as the glomerular blood hydrostatic pressure (GBHP), which is responsible for filtering fluid and molecules out of the glomerular capillaries into the tubular lumen of the nephron[13]. According to Pottel (2017), approximately 120 ml of plasma is filtered in the glomerulus per minute to maintain the glomerular filtration rate in the kidneys[14]. On the other hand, a study by Milanesi et al. (2019) described that angiotensin II-mediated vasoconstriction regulates intraglomerular pressures, whereas renal prostaglandins regulate afferent arterioles' pressure[15].

Decreased blood flow to the kidney activates the renin-angiotensin system resulting in a rise in angiotensin II. As a result, the glomerular capillary pressure is increased to maintain the glomerular filtration rate[9]. A research study by Sudjarwo et al. (2019) highlighted that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) block the action of angiotensin activation lowering glomerular capillary pressure[16]. Although this mechanism could be effective in patients with diabetes, in states of volume laws and decreased kidney perfusion, the use of ACEIs may eventually decrease glomerular pressure and glomerular filtration rate (GFR). Therefore, the condition of hypo-perfusion will be prevalent in such cases, where the amount of blood filtered is reduced[17]. However, prostaglandins may preserve kidney perfusion during volume depletion and GFR by vasodilating the afferent arteriole. However, medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) that act as prostaglandin antagonists eventually prevent prostaglandin functioning and contribute to the deterioration of glomerular pressure and reduced GFR, as described by Lucas et al., (2018)[18]. This glomerular dysfunction results in the pre-renal cause for nephrotoxicity[19].

Renal tubular toxicity

The majority of the glomerular filtrate is reabsorbed by first segment of the kidneys' nephrons, also known as proximal renal tubules[20]. Proximal tubule cells are susceptible to drug-induced toxicity due to their alternative active secretion and reabsorption[21]. A wide range of metabolic enzymes and functional transporters integrated within the epithelium of the proximal tubule tend to assist the process of renal drug elimination[20]. Therefore, the proximal renal tubule plays a significant part in eliminating waste products such as drugs and their toxic metabolites from the human body[21]. However, due to renal reabsorption of the toxic metabolites, the tubular cells of the proximal renal tubule are kept in continuous contact with the drugs[15]. A study by Vormann et al. (2018) explained that the prolonged concentration process and exposure of the proximal tubule cells to certain medications such as antivirals, amphotericin B, and aminoglycoside cause damage to the proximal tubules[20]. The

oxidative stress is increased due to free radical generation by these drugs, which eventually cast damage to tubular mitochondria, inhibit phosphorylation, disturb the Ca^{+2} homeostasis, and disturb the renal tubular transport system. These circumstances contribute to the development of cell cytotoxicity[22].

Due to the injury of tubular cells by the toxicants, the permeability of the proximal tubules is eventually increased, which will allow more filtrate to leak back into the interstitial. The filtrate leakage into the circulation further lowers the GFR[18]. As the proximal tubules host a higher level of cytochrome P-450 to detoxify or activate toxicants, it turns proximal tubules into the most vulnerable site of toxic effects[23]. On the other hand, some particular toxicants may even enhance the adhesion among the tubular cells forcing them to obstruct the reabsorption pathway for the filtrate. The condition of hyperfiltration will be prevalent due to the reduced amount of filtrate reabsorbed[24]. The resistance of the filtrate movement into the tubule increases the pressure within the proximal tubule as the tubular cells are damaged. The rendered functioning of the proximal tubule and tubular cytotoxicity ultimately results in nephrotoxicity[13].

Nephron inflammation

Drugs associated with nephrotoxicity may also result in an inflammation of several kidney parts, such as the proximal tubules, glomerulus, and intracellular matrix[20]. This inflammation can gradually extend to fiberize the kidney tissues as well. A study by Tjon and Teoh (2020) indicated that glomerulonephritis and interstitial nephritis are significant inflammation forms that tend to induce renal toxicity and disturb normal kidney functioning[25]. While glomerulonephritis is associated with injury in the glomerular portion of the nephron, interstitial nephritis is associated with swollen spaces between the kidney tubules[3]. Certain drugs, including analgesics, calcineurin inhibitors, and anticancer drugs, are observed to be contributing to the development of chronic interstitial nephritis[26]. The renal cell cytotoxicity and decline in kidney efficiency due to inflammation eventually lead to nephrotoxicity. Simultaneously, prolonged interstitial nephritis may also lead to complete loss of kidney function.

Crystal nephropathy

The term "nephropathy" is associated with the deterioration of kidney function. Based on this definition, crystal nephropathy is the decline in kidney function due to crystal formation in the renal structure[18]. According to Pawar and Vyawahare (2015), several drugs such as ampicillin, ciprofloxacin, sulfonamides, ampicillin, and triamterene are insoluble in the human urine, resulting in intratubular crystal[8]. However, drug concentration and urine acidity are collective contributory factors in determining the formation of insoluble crystals. The appearance of crystals in the distal renal tubules may eventually cause an interstitial reaction and even obstruct the filtrate pathway. This leads to crystal nephropathy, which is more prevalent in patients with renal impairment[27]. As a result of an obstruction in the renal structure, kidneys may suffer from nephrotoxicity. Tumor lysis performed due to the chemotherapy induction, another form of medication treatment, may also lead to deposition of uric acid leading to kidney failure[28].

Rhabdomyolysis

Cabral et al. (2020)[22] described rhabdomyolysis as a life-threatening syndrome in which skeletal muscle fibers are broken down, and the intracellular muscle contents start to leak into the

surrounding circulation. There are several potential causes of rhabdomyolysis that could be categorized into three categories as follows:

1. Direct muscle tissue damage due to blunt/crush trauma to tissues, compartment syndrome, ischemia, and hyperthermia[29].
2. Metabolic damage to muscles due to ATP depletion (seizures, high-intensity exercise, thyroid disorders) and electrolyte disorders [22].
3. Drugs and toxins damage muscles. Medications including sympathomimetic, anticholinergics, and antihistamines that result in hyperthermia can also induce rhabdomyolysis. Toxic alcohol is another reason for the development of rhabdomyolysis. Simultaneously some prescription medications such as statin may also cause Rhabdomyolysis[30].

Myocyte lysis in the renal tissues due to any of the causes mentioned above may contribute to rhabdomyolysis as it releases intracellular contents such as serum creatine kinase and myoglobin into blood plasma[31]. The myoglobin released into the blood eventually degrades and obstructs the normal filtration functioning of the kidney. In addition, myoglobin induces renal injury as it casts oxidative stress endothelial dysfunction vasoconstriction and apoptosis. This condition results in nephrotoxicity, renal failure, or acute tubular necrosis[32].

Thrombotic microangiopathy

A study by Shatzel and Taylor (2017) describes thrombotic microangiopathies as any clinical syndrome or disease process which results from thrombosis in arterioles or capillaries due to a severe injury to the endothelium[33]. Although several factors contribute to the epithelial damage, drug-induced thrombotic microangiopathy in kidneys tends to be a significant cause of nephrotoxicity. According to Brocklebank et al (2018)[26], and Shatzel, and Taylor, (2017)[33] certain drugs such as quinine and cyclosporine are responsible for direct toxicity in renal epithelial cells or cause tubular inflammation, which activates the immune response, as a result, the platelets start to aggregate at the side of the injury. The platelet clusters in the renal epithelial walls eventually narrow down the lumen of the renal capillaries even further. These clusters could cause damage to the passing red blood cells leading to thrombotic thrombocytopenic purpura. In this condition, small blood clots (thrombi) are formed in blood vessels[26]. This condition leads to endothelial cytotoxicity and eventually nephrotoxicity[33].

Patient-related risk factors

Studies have revealed several risk factors of drug-induced nephrotoxicity associated with the patients, such as age, gender, pre-existent renal disease, and prevalence of other specific disorders[34]. Patients older than 60 years are considered to be at a higher risk of developing drug-induced nephrotoxicity due to thirst impairment and altered water and sodium homeostasis[9]. In addition, the risk of nephrotoxicity among elderly patients is increased if they are suffering from diabetes mellitus, an underlying chronic renal impairment, dehydration, and cardiovascular disease[34]. Gender is considered another contributory factor in the possibility of drug-induced nephrotoxicity as studies have revealed that males are at a higher risk to experience nephrotoxic effects rather than females due to differences in hormones[35]. Hepatic insufficiency, another specific disorder, may also contribute as a risk factor for nephrotoxicity[36].

Potential drugs associated with nephrotoxicity

A wide range of drugs has the potential to induce nephrotoxicity among

patients under different circumstances. Examples are antibiotics (aminoglycoside, vancomycin), antifungal (amphotericin B), antidepressants (amitriptyline, fluoxetine), antiviral (acyclovir), antihypertensive (ACEIs, ARB, diuretics), NSAIDs/ COX2 inhibitor, cocaine, heroin, ketamine, statins, and antihistamines (diphenhydramine) are described as follows:

1. Antibiotics and antifungal medications such as amphotericin B promote tubular cell cytotoxicity by increasing oxidative stress, impairing mitochondrial function, and interfering with tubular transport[37].
2. An aminoglycoside such as streptomycin, gentamycin, kanamycin, and neomycin majorly impact the proximal tubules. Aminoglycosides tend to accumulate in the epithelial cells of the proximal tubule due to the presence of multi-ligand receptor megalin. These antibiotics also alter certain other features of proximal tubules such as membrane phospholipid composition, permeability, adenylyl cyclase activity, and transport of ions such as K^{+}, Ca^{+2}, and Mg^{+2}. Moreover, the selective endocytosis triggered by the aminoglycoside eventually affects the proximal tubule epithelial cells[37].
3. Statin, alcoholism, methadone, methamphetamine, fluoxetine, diphenhydramine, and cocaine contribute to rhabdomyolysis[38].
4. NSAIDs such as diclofenac tend to constrict afferent arteriole of the glomerular capillaries resulting in kidney damage[3].
5. ACEIs such as captopril and ARBs like valsartan also deteriorate the intraglomerular pressure[19].
6. Acetaminophen, along with NSAIDs, may lead to nephrotoxicity by altering the intraglomerular pressure and acute interstitial nephritis, chronic interstitial nephritis, and glomerularnepritis[3].
7. Anticancer drugs, including foscarnet and cisplatin, and anti-retroviral drugs like adefovir tend to induce renal tubular cell cytotoxicity leading to nephrotoxicity[39].
8. Certain antiplatelet drugs such as ticlopidine, cyclosporine, quinine, and mitomycin-C tend to induce thrombotic microangiopathy in renal capillaries' leading to nephrotoxicity[3].
9. Radiocontrast media could be a contributor to nephrotoxicity among patients who are on metformin prescription. At the same time, metformin is a common medication prescribed to patients who have type 2 diabetes. Therefore, receiving radiocontrast media simultaneously with metformin could lead to nephrotoxicity[40].
10. Lithium salts, antibiotics (rifampicin), NSAIDs, and calcineurin inhibitors can trigger interstitial nephritis leading to nephrotoxicity[3].
11. Certain drugs insoluble in human urine like methotrexate, ciprofloxacin, acyclovir, triamterene, and sulfonamides are responsible for the development of crystal nephropathy leading to Nephrotoxicity[41].

Drug-related risk factors

Studies have revealed that prolonged exploration of certain drugs, such as allopurinol, may eventually increase the risk of developing crystal nephropathy and chronic interstitial nephritis[19]. Pre-renal nephrotoxicity, obstructive nephrotoxicity as well as acute tubular necrosis are drug dose-dependent diseases. Based on this evidence, the drug-related risk factors of nephrotoxicity could be interpreted as the dose duration and frequency of administration[19]. These two factors tend to determine the drug's pharmacokinetics, its half-life, and the period of stay within the body of an individual. Vahed et al., (2015) highlight that the risk of renal damage is increased when a particular combination of nephrotoxic medications is prescribed to a patient, such as diuretics[36]. Such as prolonged combined drug treatment of aminoglycosides and amphotericin

increases the risk of developing Nephrotoxicity. Another drug-related risk factor is the hypersensitivity sensitivity to allergic reaction, which leads to Acute interstitial nephritis (AIN)[19].

Preventing drug-induced renal impairment

Renal impairment is associated with poor kidney functioning due to renal injury or reduced blood through the kidneys. Drug-induced nephrotoxicity tends to contribute to about 18-27% of all cases of acute kidney injury. For the prevention of drug-induced renal impairment, specific steps need to be considered, such as:

1. Strict evaluation and assessment of the risk factors of nephrotoxicity related to the patient and the drug being prescribed to the patient[4].
2. Recommending alternative therapies for patients at higher risk of developing nephrotoxicity, for example, adjusting the drug dosage according to the patient's renal function[19].
3. Avoid nephrotoxic combination[4].
4. Ensure adequate hydration before and during therapy[19].
5. Use equally effective non-nephrotoxic drugs whenever possible[4].
6. Assessment of kidney functioning must be carried out before and during the treatment to early recognize kidney injury[42]. Effects of kidney damage are frequently assessed in non-specific aspects such as proteinuria (increased protein content in urine), altered kidney weight than expected normal range, and changes in urine volume such as polyuria, oliguria, and anuria. In case of oliguria ensure assessed, along with a raised level of eosinophils, the drug must be discontinued, or the water consumption must be increased (150-250 mL/hour)[42].
7. Assessments for drug-induced nephrotoxicity and designing preventive measures following the evaluation. The most common clinical manifestations of drug-induced nephrotoxicity are the rise in blood urea nitrogen and serum creatinine due to reduced glomerular filtration rate[4].
8. Treating patients demonstrating symptoms of nephrotoxicity. For patients suffering from TTP (thrombotic thrombocytopenic purpura), plasmapheresis therapy could be recommended. For patients suffering from obstructive nephrotoxicity, drugs including indinavir, triamterene, sulfonamides, and methotrexate must be highly avoided. Urine alkalization is recommended where the patient must intake less acidic foods and proteins[43].

CONCLUSION

Although nephrotoxicity is a disease induced mainly by prescribed medications, adopting specific preventive measures could prevent patients, especially elders, from the chronic effects of nephrotoxicity. Drugs which intrinsically cause nephrotoxicity, however, when paired with patient-associated risk factors, their vulnerability increases. Therefore, it is necessary to assess the renal function of the underlying patient and adjust their medication and its dose according to their necessities. Moreover, a combination of nephrotoxic drugs results in synergistic nephrotoxicity, which must be avoided by changing the drug with a non-nephrotoxic medication or suggesting altered therapies.

REFERENCES

[1] Health Policy Institute. Prescription drug statistics 2022. Published 2021. https://www.singlecare.com/blog/news/prescription-drug-statistics/

[2] Al-Naimi M, Rasheed H, Hussien N, Al-Kuraishy H, Al-Gareeb A. Nephrotoxicity: Role and significance of renal biomarkers in the early detection of acute renal injury.

Journal of Advanced Pharmaceutical Technology and Research. 2019;10(3):95-99. doi:10.4103/japtr.JAPTR_336_18

[3] Kim SY, Moon A. Drug-induced nephrotoxicity and its biomarkers. Biomolecules and Therapeutics. 2012;20(3):268-272. doi:10.4062/biomolther.2012.20.3.268

[4] Miyahara T. Drug-induced renal disorders. Nippon rinsho Japanese journal of clinical medicine. 1978;Suppl(3):2320-2321. doi:10.12861/jrip.2015.12

[5] Wang X, Bonventre J V., Parrish AR. The aging kidney: Increased susceptibility to nephrotoxicity. International Journal of Molecular Sciences. 2014;15(9):15358-15376. doi:10.3390/ijms150915358

[6] Mohamed F, Endre ZH, Buckley NA. Role of biomarkers of nephrotoxic acute kidney injury in deliberate poisoning and envenomation in less developed countries. British Journal of Clinical Pharmacology. 2015;80(1):3-19. doi:10.1111/bcp.12601

[7] Washinger K. Acute Kidney Injury in Adults: An Underdiagnosed Condition. Journal for Nurse Practitioners. 2017;13(10):667-674.e1. doi:10.1016/j.nurpra.2017.08.005

[8] Pawar A, Vyawahare N. Anti-urolithiatic activity of standardized extract of Biophytum sensitivum against zinc disc implantation induced urolithiasis in rats. Journal of Advanced Pharmaceutical Technology and Research. 2015;6(4):176-182. doi:10.4103/2231-4040.165017

[9] Koch CA, Fulop T. Clinical aspects of changes in water and sodium homeostasis in the elderly. Reviews in Endocrine and Metabolic Disorders. 2017;18(1):49-66. doi:10.1007/s11154-017-9420-5

[10] Hugh Rayner MT& DM. Kidney Anatomy and Physiology. In: Understanding Kidney Diseases. ; 2015:1–10.

[11] Secomb TW. Hemodynamics. Comprehensive Physiology. 2016;6(2):975-1003. doi:10.1002/cphy.c150038

[12] Diabetes in T 2 IDPKF, Bjornstad PJSHCLMMBNEGSRRGNP. Intraglomerular Dysfunction Predicts Kidney Failure in Type 2 Diabetes. Diabetes. 2021;70(10):2344–2352. doi:https://doi.org/10.2337/db21-0154

[13] Tsuda A, Ishimura E, MacHiba Y, et al. Increased Glomerular Hydrostatic Pressure is Associated with Tubular Creatinine Reabsorption in Healthy Subjects. Kidney and Blood Pressure Research. 2020;45(6):996-1008. doi:10.1159/000510838

[14] Pottel H. Measuring and estimating glomerular filtration rate in children. Pediatric Nephrology. 2017;32(2):249-263. doi:10.1007/s00467-016-3373-x

[15] Milanesi S, Verzola D, Cappadona F, et al. Uric acid and angiotensin II additively promote inflammation and oxidative stress in human proximal tubule cells by activation of toll-like receptor 4. Journal of Cellular Physiology. 2019;234(7):10868-10876. doi:10.1002/jcp.27929

[16] Sudjarwo SA, Eraiko K, Sudjarwo GW, Koerniasari. The potency of chitosan-Pinus merkusii extract nanoparticle as the antioxidant and anti-caspase 3 on lead acetate-induced nephrotoxicity in rat. Journal of Advanced Pharmaceutical Technology and Research. 2019;10(1):27-32. doi:10.4103/japtr.JAPTR-306-18

[17] Extreme P. Biochemical Markers of Renal Hypoperfusion ,. :1-11.

[18] Lucas GNC, Leitão ACC, Alencar RL, Xavier RMF, Daher EDF, Silva Junior GB da. Pathophysiological aspects of

nephropathy caused by non-steroidal anti-inflammatory drugs. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2019;41(1):124-130. doi:10.1590/2175-8239-JBN-2018-0107

[19] Bicalho MD, Soares DB, Botoni FA, Reis AMM, Martins MAP. Drug-induced nephrotoxicity and dose adjustment recommendations: Agreement among four drug information sources. International Journal of Environmental Research and Public Health. 2015;12(9):11227-11240. doi:10.3390/ijerph120911227

[20] Vormann MK, Vriend J, Lanz HL, et al. Implementation of a Human Renal Proximal Tubule on a Chip for Nephrotoxicity and Drug Interaction Studies. Journal of Pharmaceutical Sciences. 2021;110(4):1601-1614. doi:10.1016/j.xphs.2021.01.028

[21] Li S, Zhao J, Huang R, et al. Current Chemical Genomics and Translational Medicine Development and Application of Human Renal Proximal Tubule Epithelial Cells for Assessment of Compound Toxicity. Current Chemical Genomics and Translational Medicine. 2017;11:19-30. doi:10.2174/221398850171101001

[22] Cabral BMI, Edding SN, Portocarrero JP, Lerma E V. Rhabdomyolysis. Disease-a-Month. 2020;(xxxx). doi:10.1016/j.disamonth.2020.101015

[23] Imig JD, Khan MAH. Cytochrome P450 and lipoxygenase metabolites on renal function. Comprehensive Physiology. 2016;6(1):423-441. doi:10.1002/cphy.c150009

[24] Magnusson O. Investigating flow-related effects of Chronic Kidney Disease on renal drug toxicity in a human-derived proximal tubule microphysiological system. Published online 2020. www.chalmers.se

[25] Tjon J, Teoh CW. Medication-Induced Nephrotoxicity in Children. Current Pediatrics Reports. 2020;8(3):122-133. doi:10.1007/s40124-020-00223-8

[26] Haller H. Thrombotic microangiopathy and the kidneys. Nephrologe. 2019;14(2):100-107. doi:10.1007/s11560-019-0320-4

[27] Sigurjonsdottir VK, Runolfsdottir HL, Indridason OS, Palsson R, Edvardsson VO. Impact of nephrolithiasis on kidney function. BMC Nephrology. 2015;16(1):1-7. doi:10.1186/s12882-015-0126-1

[28] Nicolaysen A. Nephrotoxic Chemotherapy Agents: Old and New. Advances in Chronic Kidney Disease. 2020;27(1):38-49. doi:10.1053/j.ackd.2019.08.005

[29] Furman J. When exercise causes exertional rhabdomyolysis. Journal of the American Academy of Physician Assistants. 2015;28(4):38-43. doi:10.1097/01.JAA.0000458861.78559.3b

[30] Rawson ES, Clarkson PM, Tarnopolsky MA. Perspectives on Exertional Rhabdomyolysis. Sports Medicine. 2017;47(s1):33-49. doi:10.1007/s40279-017-0689-z

[31] Bäcker HC, Busko M, Krause FG, Exadaktylos AK, Klukowska-Roetzler J, Deml MC. Exertional rhabdomyolysis and causes of elevation of creatine kinase. Physician and Sportsmedicine. 2020;48(2):179-185. doi:10.1080/00913847.2019.1669410

[32] Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Critical Care Medicine. 2008;36(SUPPL. 4).

doi:10.1097/CCM.0b013e318168e375

[33] Shatzel JJ, Taylor JA. Syndromes of Thrombotic Microangiopathy. Medical Clinics of North America. 2017;101(2):395-415. doi:10.1016/j.mcna.2016.09.010

[34] Prasaja Y, Sutandyo N, Andrajati R. Incidence of cisplatin-induced nephrotoxicity and associated factors among cancer patients in Indonesia. Asian Pacific Journal of Cancer Prevention. 2015;16(3):1117-1122. doi:10.7314/APJCP.2015.16.3.1117

[35] Chen WY, Hsiao CH, Chen YC, et al. Cisplatin nephrotoxicity might have a sex difference. an analysis based on women's sex hormone changes. Journal of Cancer. 2017;8(19):3939-3944. doi:10.7150/jca.20083

[36] Vahed SZ, Ardalan M, Samadi N, Omidi Y. Pharmacogenetics and drug-induced nephrotoxicity in renal transplant recipients. BioImpacts. 2015;5(1):45-54. doi:10.15171/bi.2015.12

[37] McWilliam SJ, Antoine DJ, Smyth RL, Pirmohamed M. Aminoglycoside-induced nephrotoxicity in children. Pediatric Nephrology. 2017;32(11):2015-2025. doi:10.1007/s00467-016-3533-z

[38] Matsubara A, Oda S, Akai S, Tsuneyama K, Yokoi T. Establishment of a drug-induced rhabdomyolysis mouse model by co-administration of ciprofloxacin and atorvastatin. Toxicology Letters. 2018;291:184-193. doi:10.1016/j.toxlet.2018.04.016

[39] Małyszko J, Kozłowska K, Kozłowski L, Małyszko J. Nephrotoxicity of anticancer treatment. Nephrology Dialysis Transplantation. 2017;32(6):924-936. doi:10.1093/ndt/gfw338

[40] Ward DB, Valentovic MA. Contrast induced acute kidney injury and direct cytotoxicity of iodinated radiocontrast media on renal proximal tubule cells. Journal of Pharmacology and Experimental Therapeutics. 2019;370(2):160-171. doi:10.1124/jpet.119.257337

[41] Wiczer T, Dotson E, Tuten A, Phillips G, Maddocks K. Evaluation of incidence and risk factors for high-dose methotrexate-induced nephrotoxicity. Journal of Oncology Pharmacy Practice. 2016;22(3):430-436. doi:10.1177/1078155215594417

[42] Wu H, Huang J. Drug-Induced Nephrotoxicity: Pathogenic Mechanisms, Biomarkers and Prevention Strategies. Current Drug Metabolism. 2018;19(7):559-567. doi:10.2174/1389200218666171108154419

[[43] Sayani FA, Abrams CS. How I treat refractory thrombotic thrombocytopenic purpura. Blood. 2015;125(25):3860-3867. doi:10.1182/blood-2014-11-551580