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An Overview on Impact of Phthalates on the Kidney and the Potential Therapeutic Effect of Drug Modalities

Omnia M. Mohamed, Asmaa A.A. Kattaia and Nahla E. Ibrahem

Department of Medical Histology and Cell Biology, Faculty of Medicine, Zagazig University, Egypt.
Corresponding Author: Omnia Mansour Mohamed
Email address: mone_hinata@ yahoo.com

Abstract:

Background: Phthalates are the most widely used plasticizers, and their usage has grown dramatically over the past few decades. The world's production of phthalates grew sharply between 2007 and 2017. The exposure to and health hazards of phthalates have drawn a lot of attention. The kidney is the central organ responsible for maintaining body water homeostasis through urine concentration and dilution. In healthy people, the renal tubules and collecting ducts reabsorb 99% of the water in the initial urine filtered through the glomeruli. Water reabsorption in these renal tubules is essential for maintaining body water homeostasis. Kidney damage is one of the hallmarks of chronic kidney disease (CKD). Chronic kidney disease (CKD) is characterized by a progressive loss of kidney function, which is frequently needed for renal replacement treatment like dialysis or transplantation. The cornerstone of CKD pharmacological treatment at the moment is to slow its progression. However, novel drugs would be extremely beneficial in effectively slowing the progressive loss of renal function.

Keywords: Phthalates, EDCs, Kidney, Drug Therapy.

Introduction:

Endocrine disrupting chemicals (EDCs) are exogenous substances that alter an organism's endocrine functions, resulting in detrimental impacts on metabolism, growth, development, and reproduction [1].

EDCs are a diverse group of chemicals derived primarily from pesticides, detergents, surfactants, phthalates, alkylphenols, and various types of natural or synthetic estrogens. Among the EDCs', phthalates are industrial chemicals that have been widely used for many years. Annually, the global plastics industry consumes more than three million tons of various phthalates [2,3].

Stojanoska et al. [4] documented that plasticizers known as phthalates are made from phthalic acid (1,2 benzenedicarboxylic acid). Phthalates are subdivided into two groups corresponding to their molecular weight: low molecular weight phthalates, which include dimethyl phthalate (DMP), diethyl phthalate (DEP), and di-n-butyl phthalate (DnBP); and high molecular weight phthalates, which include di-(2- ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DINP), and diisodecyl phthalate (DIDP).

Phthalates exist in a wide range of products, including intravenous bags, infusion tubes, dialysis bags, dyes, insect repellent, hair spray, shampoo, personal hygiene and cosmetics, food packaging, medical devices (such as intravenous tubing and medications), and construction materials [5].

Martínez-Ibarra et al. [6] revealed that the majority of commercial products use phthalates as additives, and they are not chemically bonded (formed covalent bonds) to the polymer matrix. Consequently, phthalates can

be progressively discharged into the environment through leaching, evaporation, and abrasion. Additionally, from the time of manufacture to disposal, phthalates' semi-volatile nature makes it easier for them to migrate or emit from phthalate-containing products into the air, soil, water, or other media.

Zhang et al. [7] postulated that food-packaging films, lid gaskets, conveyor belts, gloves used in food preparation, and tubing commonly used in the milking process are examples of plasticized PVC materials that can release phthalates into food. These substances can also be found in food wrapper printing inks and adhesives, as well as coatings on cookware that have been tainted by food packaging.

Ma et al. [8] stated that individuals are exposed to phthalates through three main routes: ingestion, inhalation, and dermal absorption. Exposure through dietary ingestion can occur through consumption of contaminated food or through infrequent dust ingestion, as high concentrations of phthalates have been found in indoor dust.

Children are more vulnerable to food poisoning than adults. While, they have more contact with polluted soil, indoor dust, and products**.** It was reported that percutaneous absorption of phthalates reached 4.5 μg/kg-Bw/day for children's toys and hand-to-mouth ingestion of phthalates was 2×10^{-3}-0.49 μg/kg-Bw/day. Also, it was found that children could be exposed to up to 37.5 μg/kg/day [9,10,11,12].

Dermal absorption of phthalates includes direct air-to-skin transport, intentional or unintentional contact with contaminated surfaces or objects, and use of phthalate-containing personal care products (PCPs). The use of shower gel, hand cream, toothpaste, anti-wrinkle cream, and shaving products are the most common sources of dermal exposure [13,14].

After entering the body, they undergo hydrolysis in the biota to produce secondary metabolites and their corresponding monoester metabolites, which are the primary metabolites and are catalyzed by intestinal lipases. Within 24 to 48 hours of exposure, the majority of these metabolites are quickly eliminated in the urine and feces. The remaining phthalates may be stored in meconium in infants or adipose tissue in adults, and they may be circulated to organs such as the liver, brain, or gonads [15,16].

Lucaccioni et al. [17] mentioned that phthalates are becoming more prevalent, and while their effects are unavoidable throughout life, they are most sensitive during the fetal, perinatal, and early childhood stages, when they have an impact on physiological parameters for the rest of the person's life

Exposure to phthalates is linked to negative developmental outcomes, including skeletal, visceral, and external malformations, decreased growth and birth weight, and increased prenatal mortality. Phthalates have a variety of effects on humans, ranging from changes in the expression of genes to changes in the whole-body physiology. Also, exposure to high molecular weight phthalates alters the methylation status of imprinted genes, which may have a direct bearing on spermatogenesis, protein secretion, estrogen response, and androgen response [18].

Based upon data from the National Health and Nutrition Examination Survey (NHANES). Phthalates can cause their harmful effects through oxidative stress and inflammation. Human health is at risk from phthalates. Phthalates are environmental endocrine disruptors that impair neurological development, immunological response, reproductive function, cardiovascular disease, and nearly every system and organ in the body. Thus, it is mandatory to reduce phthalate exposure in the environment [19, 20].

Hegazy et al. [21] reported that the extracellular fluid is maintained by the metabolically active kidney. Additionally, kidney is susceptible to drugs that interfere with metabolism. They are in charge of removing a lot of free radicals and harmful substances. Either disrupted antioxidant enzyme activity or decreased expression of these enzymes in the kidneys can result in renal damage. Environmental nephrotoxicants, such as phthalates, can

affect the kidney.

Huang et al. [22] demonstrated that high Phthalate exposure causes tubular degeneration, CKD, kidney tubular damage, and decreased kidney weight. These effects could be explained by changes in the protein expression of peroxisome proliferator–activated receptor (PPAR) gamma (PPARγ), an increase in inflammatory cytokines in blood serum, and inhibition of the Nrf2 signaling pathway in the mouse kidney.

Anatomically, the kidney is a vital structure of the endocrine system. The paired kidneys are reddish, bean shaped organs. It is located in the retroperitoneally between the levels of the last thoracic 12th and 3rd lumbar vertebrae. Kidney weighs approximately 135-150 gram. the medial surface is concave and features a slit called the hilum through which the ureter, blood vessels, lymphatics, and renal nerves are received, the lateral surface is convex. The hilum and renal sinus are connected internally**.** All structures are encircled by perinephric fat, which extends into the sinus and hilum**.** The kidney consists of cortex and medulla **Fig. (I).** [23, 24].

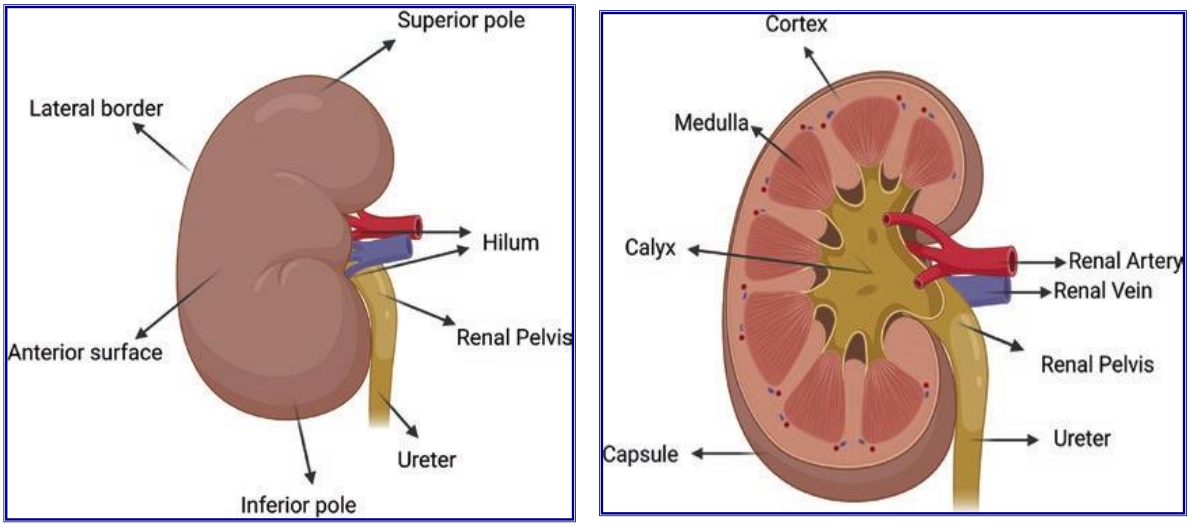

Fig. (I): Anatomy of kidney [25].

Physiologically, Nephrons are the fundamental structural and functional units of the kidney. The glomerulus and the renal tubule are its two constituent parts. The glomerulus carries out filtration, while the renal tubule carries out reabsorption and secretion, which are the three main processes by which the nephron separates the different components of blood [26].

Through the renal arteries, the kidney receives 20–25% of cardiac output, or more than 1 liter of blood per minute. The renal cortex receives more than 90% of this, while the medulla receives the remaining portion. Twenty percent of the 600–650 ml/min renal plasma flow (RPF) is filtered into Bowman's capsule via the glomerular filtration barrier (GFB). This filtration rate is known as the glomerular filtration rate (GFR), and in a healthy person, it ranges from 100 to 140 milliliters per minute (**Fig.II).** [27, 28].

Sahay et al. [29] reported that the kidney has multiple endocrine roles. In detail, the kidney secretes a variety of humoral factors and hormones, including erythropoietin (EPO), renin-angiotensin system (RAS) hormones, and 1,25 dihydroxy vitamin D3.

Erythropoiesis, or the production of red blood cells, is regulated by the hormone erythropoietin (EPO), which is produced by fibroblasts in the renal cortex. Renin is a protease that cleaves angiotensinogen to angiotensin I, catalyzing the renin-angiotensin system's rate-limiting step. The juxtaglomerular cells secrete it. The angiotensin-converting enzyme subsequently transforms angiotensin I into angiotensin II, which causes vasoconstriction, aldosterone secretion, sodium reabsorption, water retention, and an increase in the production

of antidiuretic hormones [30,31].

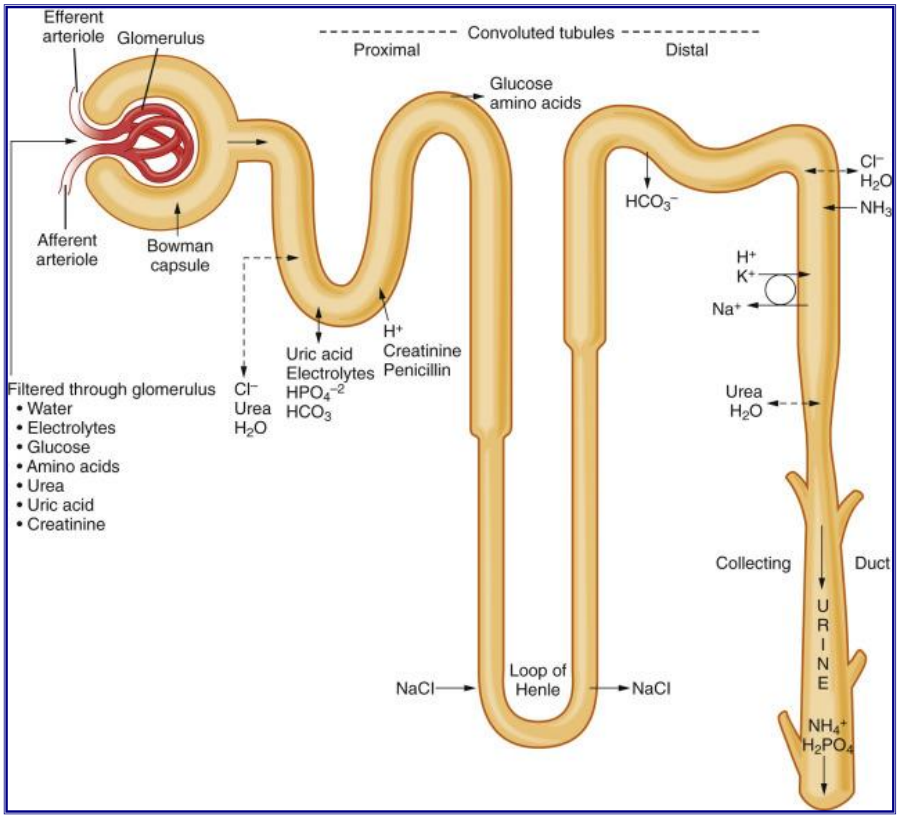

Fig.II: A diagram showing physiological function of the kidney [28].

Embryologically, the vertebrate kidney develops in three structurally separate stages beginning with a non-functional pronephros, progressing to a rudimentary mesonephros, and finally to the metanephros, which persists as the adult kidney. Nephrogenesis is a process that lasts until the 32nd week of pregnancy. It repeats radially, with the first nephrons developing in the juxtamedullary regions and the last in the peripheral cortex, until the full complement of nephrons is reached **(Fig.III).** [32,33, 34].

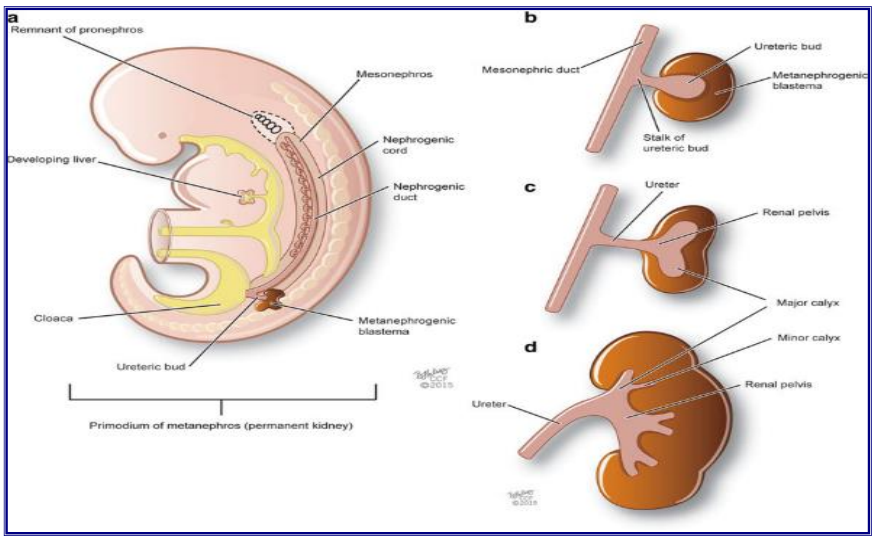

Fig.III: A diagram showing embryology of kidney [35].

Kalantar-Zadeh et al. [36] reported that the progressive condition known as chronic kidney disease is distinguished by alterations in the kidney's structure and function that can arise from a variety of causes. The prevalence of chronic kidney disease is high and on the rise; 10% of adults worldwide suffer from some form of the condition. Chronic kidney disease is predicted to rise at one of the fastest rates of any major cause of death by 2040, ranking as the fifth most common cause of death worldwide.

Chronic kidney disease (CKD) is a deadly condition that is affecting society more and more. Kidney failure is one of the most fatal and expensive illnesses that patients and contemporary society must deal with. With over 70% of diabetic patients dying within five years and over 20% of patients dying within the first year after beginning dialysis, the prognosis for end-stage renal disease (ESRD) is worse than that of most cancers. Nevertheless, less than 10% of patients even know they have early chronic kidney disease (CKD), and a comparable percentage of doctors do not diagnose CKD when it is present [37].

The majority of people with CKD are over 65, but younger individuals (≤65 years old) with CKD have a higher chance of developing ESRD. It's interesting to note that men are more likely to develop ESRD than women, despite the fact that women are more likely to have CKD. Diabetes mellitus and hypertension are the most prevalent underlying conditions linked to chronic kidney disease (CKD), especially in high- and middle-income nations [38].

Additionally, since the 1980s, there has been a steady rise in the incidence and prevalence of CKD in children. End-stage renal disease (ESRD), which has a substantial impact on morbidity, mortality, and healthcare expenses, can develop from chronic kidney disease (CKD) and require a kidney transplant or renal replacement treatment (for instance, dialysis) [5].

The body's physiological processes, such as blood pressure regulation, toxin excretion, vitamin D metabolism, and water and electrolyte balance, are all disrupted by this illness. GFRs of below sixty mL/min/1.73 m2 for a period of time exceeding three months, or GFRs exceeding 60 mL/min/1.73 m2 but with particular signs of kidney damage, are indicating this disease [39].

Currently, drugs are used to treat patients with CKD, include angiotensin-converting enzyme inhibitors, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors. Angiotensin-converting enzyme inhibitors are regarded as a first-line anti-hypertensive treatment for hypertension symptoms in cardiovascular and coronary diseases. Additionally, sulfonylureas act on pancreatic β cells via depolarizing the Ca+2 channels. Finally, DPP-4 inhibitors improve endothelial dysfunction and offer multilevel kidney protection by preventing oxidation, inflammation, and fibrosis, blocking the advanced glycation end product (AGE) signaling pathway, and increasing GLP 1 [40].

Angiotensin converting enzyme inhibitors have poor side effects, such as cough or angioneurotic edema, despite their promising qualities. Regardless of being well-tolerated medications, nearly one-fifth of patients stop taking them because of side effects, particularly coughing. According to studies conducted on various populations, the incidence of cough linked to ACE-I ranges from 3.9% to 35%. Coughing brought on by ACE-I may appear hours after the initial dosage or even weeks or months later. The cough is more common in women and nonsmokers [41].

Conversely, short-acting sulfonylureas are often used, their risk of hypoglycemia is higher than that of other medications. Upper respiratory tract infections, nasopharyngitis, headaches, urinary tract infections, arthralgia, anaphylaxis, angioedema, and Stevens-Johnson syndrome are among the unfavorable adverse effects of DPP-4 inhibitors [42, 43].

Hurren and **Dunham, [44]** showed that with the lack of effects beyond these drugs, development of novel therapeutic drugs for CKD is critical. In recent head-to-head trials, the new drug Pioglitazone has proven

more effective than sulfonylureas and dipeptidyl-peptidase-4 (DPP4) inhibitors due to its low cost and beneficial effects. Consequently, Pioglitazone holds promises for improved outcomes among CKD patients.

The thiazolidinediones family includes Pioglitazone (5 [[4 [2 (5 ethylpyridin 2 yl) ethoxy] phenyl] methyl] 1,3 thiazolidine 2,4 dione;hydrochloride). thiazolidinediones (TZDs), synthetic exogenous agonists of the nuclear peroxisome as well as proliferator-activated receptor-gamma (PPARγ), have anti-inflammatory and other advantageous vascular effects in addition to increasing insulin sensitivity and inhibiting adipose tissue lipolysis. The liver metabolizes TZDs, which have been demonstrated to function effectively without increasing the risk of hypoglycemic strikes in patients with chronic kidney disease. Even hemodialysis has no effect on the pharmacology of TZDS' profile, which is comparable in subjects with normal or impaired renal function. Consequently, patients with CKD do not need to change their TZD dosage [45,46].

Saha et al. [47] reported that Pioglitazone, as the most common thiazolidinedione used in clinical practice today, is an agonist of the peroxisome proliferator-activated receptor (PPAR-γ) that promotes the transcription of genes that respond to insulin, thereby increasing insulin sensitivity. It results in adipocyte differentiation and the control of lipid and carbohydrate metabolism. By encouraging the synthesis and expression of cellular glucose and fatty acid transporters, Pioglitazone promotes the uptake of glucose and fatty acids into cells.

Singh et al. [48] demonstrated that Pioglitazone is easily absorbed and takes two to four hours to reach its peak plasma time. Over 99 percent of it is protein bound. Distribution volume: 0.63 L/kg. It has a half-life of three to seven hours for elimination. It is administered once daily and is thought to have pharmacokinetic effects that last for 24 hours. CYP2C8 and CYP3A4 in the liver metabolize Pioglitazone. 15–30% of Pioglitazone and its metabolites are eliminated through urine, with the remaining amounts going into bile and feces.

By increasing the antioxidant capacity, Pioglitazone, a PPARγ agonist, can shield the kidney from ischemia-reperfusion damage. Additionally, Pioglitazone can improve renal injury brought on by metabolic syndrome through minimizing endothelial dysfunction and upregulating the expression of vascular endothelial growth factor (VEGF), which promotes angiogenesis [49].

Yen et al. [50] clarified that Pioglitazone can lower the risk of atherosclerosis and associated cardiovascular disease. In conclusion, Pioglitazone may help patients with CKD and ESRD by reducing protein energy wasting, a common complication that can lead to infection, fragility, and death. Pioglitazone's appetite-stimulating and insulin-sensitizing properties may lessen the impact of protein energy waste and further lower infection-related mortality.

Katahira et al. [51] showed that in both CKD and CVD, Pioglitazone has protective effects. In specifics, Pioglitazone reduces inflammation and improves degenerative processes such as neointimal proliferation, as well as arterial and valvular calcification, by lowering the atherosclerotic burden. Pioglitazone is therefore a promising option for treating CKD patients.

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