Microplastics Effects on Kidney Tissues and Cells

Subjects: Urology & Nephrology

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Microplastics (MPs) have become ubiquitous and humans are exposed daily to inhalation or ingestion of plastic microparticles. Studies performed using mainly spectroscopy or spectrometry-based techniques have shown astounding evidence for the presence of MPs in human tissues, organs and fluids. The placenta, meconium, breast milk, lung, intestine, liver, heart and cardiovascular system, blood, urine and cerebrovascular liquid are afflicted by MPs' presence and deposition.

microplastics kidney disease toxicity

1. Introduction

Microplastics (MPs) are defined as plastic fragments (fibers, particles or films) between 1 µm and 5 mm of size, while nanoplastics are below 1 µm. MPs can be categorized as primary or secondary. Primary MPs are small plastic pieces produced as such, while "secondary MPs" are plastic fragments deriving from the corruption and fragmentation of larger plastic pieces through physical, chemical or biological processes [1]. MPs occur in the environment through many routes: abrasion and erosion, wear and tear pf polymers, agricultural practices, industrial waste, fishing activities, garbage patches and the textile and clothing industry. Textile microfibers are one of the most important sources within primary microplastics. Laundering 6 kg of synthetic materials could release between 137–728 fibres per wash [2]. Microfibers can enter the environment throughout the supply chain of the fashion industry, from textile fabrication and clothing manufacturing to including domestic laundry activities [3]. Plastic production every year is increasing, and reached 368 million tons/year production worldwide in 2020 [4].

MPs have been detected in soil, fresh water, sea water and the atmosphere, and they have also been found in seafood, sea salt and various foods [5]. They have definitively entered into the human food cycle, becoming ubiquitous and representing an environmental threat [6]. A study performed by Cox et al. estimated an annual ingestion of 39,000–52,000 particles and a global exposition of 74,000–121,000 per year [7]. Moreover, the presence and detrimental effects of MPs in marine fauna have been demonstrated. Several studies performed on animals showed the ability of MPs to cross cell membranes and deposit on organs and tissues, causing oxidative stress, inflammation and metabolic disorders [8].

In consideration of this increasing evidence, MPs have become a growing medical concern in recent years and increasing studies have been published investigating the presence of MPs in human tissues and fluid. Surprisingly, almost the entirety of the studies showed the presence of MPs in organs and tissues analyzed such as the placenta, lungs, liver and blood, but their potential health-damaging consequences are still being debated. Moreover, an increasing amount of research on the toxicity of MPs on human cells and animal models has been carried out, and several studies into human cell lines have shown inhibition of cell growth and various molecular alterations [9]. Processes through MPs reaching organs and tissues are still a matter of research: nanoparticles can cross cellular membranes, while for bigger particles, mechanisms of endo and exocytosis are probably more involved. A pivotal role seems to be played by the formation of a coating of eco-coronas composed of biomolecules (e.g., proteins, lipids) that enhances the internalization of MPs into cells [10].

2. Microplastics Effects on Kidney Tissues and Cells

The growing concern among the medical community about the impact of MPs on human health has influenced the increasing number of studies performed in the last few years on human tissues and cells. Even though this trend refers to nephrology too, robust evidence on the effect of MPs and its compounds on kidney cells and tissues is still lacking.

Most of the studies performed on nanoplastics (NPs) and MPs' toxicity on kidney have been published in the last two years. Li et al. showed that PS-NPs worsen lipopolysaccharide-induced apoptosis in mouse kidney cells through the oxidative stress–endoplasmic reticulum pathway [11]. Furthermore, Tang et al. demonstrate nephrotoxicity in mice related to inflammation, oxidative stress and lipid disturbance [12]. After 6 weeks' exposure to PS-NPs, the murine kidney index resulted in being decreased and presented tubular atrophy, glomerular collapse and inflammatory cells' infiltration leading to decreased kidney function. Although some studies investigated NPs and MPs together, they have very peculiar characteristics due to their different size. Stability in biological solutions, formation of protein corona, absorption and intake by cell and tissues are markedly different among nano- and microparticles, making difficult comparisons between their effects in vivo and in vitro. The evidence supporting a potential toxic effect of MPs on kidneys (**Table 1**). A first pioneering study performed by Deng et al. in 2017 investigated the tissue accumulation and toxicity of PS-MPs using fluorescent microspheres of 5 and 20 µm in mice [13]. They demonstrated kidney deposition of MPs in mice. Moreover, the results showed oxidative stress, energy and lipidic metabolism alteration through metabolomic analysis. PS-MPs effects were further examined in another study in kidney tubular cells (HK2) and mice. Researchers confirmed the accumulation of MPs in kidneys in mice and uptake by HK2 [14]. Results suggested PS-MPs induce an increase in mitochondrial ROS, ER stress-related proteins, inflammation and autophagy biomarkers. Meng et al. corroborated the detrimental effects of PS-MPs in kidneys of mice through oxidative stress and inflammation. Significant increases in SOD, GSH-Px and significant inhibition of CAT in mice exposed to PS-NPs and PS-MPs were observed [15]. TNF-α, IL-6, IL-10 and MCP-1 resulted in being significantly increased too. Overall, PS-MPs seemed to cause increased mortality, weight loss and histologically proven kidney damage in mice. Meng et al. confirmed inflammation induced by PS-MPs through the activation of NF-κB in another study performed on chicken [16]. They showed that PS-MPs induce the

alteration of necroptosis via RIP1/RP3/MLKL signaling too. The activation of ROS by PS-MPs was also demonstrated by Goodman et al. in vitro on human embryonic kidney cells (HEK293) [17]. They used 1 µm PS-MPs at relevant environmental concentrations for a 24–72 h time frame. They showed significant morphological changes in HEK293 increased ROS expression and lowered gene expression of antioxidant markers (SOD2, CAT, GAPDH) indicating lowering glycolytic activity, thus the altered ability of HEK293 to contrast ROS. Altogether, these alterations affect the overall function of kidney cells. The cytotoxicity of PS-MPs has been detected on HEK293 within 24 h of exposure [18]. Oxidative stress and inflammation in kidney cells by PS-MPs could also be due to the inhibition of HO activity and induction of cytokines (IL-1β, IL-2, IL-6, TNF-α, TIMP-1 and 2) at low-noncytotoxic MPs concentration. At higher MPs' concentrations (300 ng/mL), Chen et al. showed that PS-MPs induce autophagy and can diminish inflammation via NLRP-3 inhibition [12]. Furthermore, autophagy and apoptosis have been shown to be induced by PS-MPs by activating the AMPK/ULK1 pathway via ROS [19]. Indeed, ROS/AMPK/ULK1 and Ppargc1α/Mfn2 pathways resulted in being significantly increased after conditioning with PS-MPs and Di(2-ethylhexyl)phthalate (DEPH), an environmental plastic compound frequently used to strength plastic products. In real life, MPs are frequently combined with other pollutants present in the environment or are used as plasticizers and associated with polymers in plastic industrial production. As demonstrated by Sun et al., DEPH and PS-MPs have a synergistic toxic effect on kidney cells [19]. This mechanism, also known as the "trojan horse effect", has also been investigated for organic and metallic contaminants [20]. In a mouse kidney injury model, toxicological effects of MPs combined with cadmium revealed kidney damage through oxidative stress, autophagy, apoptosis and fibrosis. In particular, 5 µm of MPs has been shown to adsorb cadmium and accumulate in the kidneys of mice inducing a severe biological response [20]: a decrease in antioxidant enzyme activities (SOD and CAT), increased autophagy markers LC3-II and autophagy early markers ATG5 and 7 and Beclin-1 and finally an increase in kidney fibrosis markers such as α-SMA, TGF-β1 and COL4A, ultimately leading to an alteration of kidney tissue structure and nephrotoxicity.

Table 1. Studies in vitro and animal models on MPs effects on kidney tissues and cell.

Author/Year	Type of Study	Conditioning Type and Time	Method Analysis	Results	Conclusion
Deng Y, 2017 [13]	In vivo study: 75 five-week-old male mice	2 types of PS microspheres (diameters 5 µm and 20 µm) – Fluorescent microspheres to quantify the accumulation and distribution –	Fluorescence spectroscopy	– No increased mortality after 4 wks – The maximal concentrations of 5 µm MPs accumulated in kidney and gut were higher than that of 20 µm MPs ($p < 0.05$)	Effects on energy metabolism, lipid metabolism, oxidative stress and neurotoxic responses

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		Treatment groups were exposed to 5 µm and 20 µm pristine PS-MPs with the exposure doses of 0.01 mg/day, 0.1 mg/day and 0.5 mg/day by oral gavage 4 weeks of exposure		– Significantly fewer 5 µm MPs were retained in liver relative to 20 µm MPs after 4 weeks of exposure ($p < 0.05$). – Inflammation and lipid droplets observed in the livers of PS-MPs-treated mice – Significant decrease in ATP level and significant increase in LDH activity in a dose dependent – Increased oxidative stress (GSH-Px and SOD increased, the activity of CAT decreased) – Significant decreases in all treatments for the levels of T-CHO and TG – Blood markers of neurotoxicity altered (AChE in liver, which decreased)	

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Wang YL, 2021 [14]	– In vitro study: human kidney proximal tubular epithelial cell line HK-2 – In vivo study: six-week-old male C57BL/6 mice	HK-2 cells 2 lm luorescent yellow-green PS-MPs at concentrations of 0.025, 0.05, 0.1, 0.2, 0.4, or 0:8 lg = mL for 120 min or at a concentration of 0:8 lg = mL for 0, 5, 10, 30 or 60 min	– Western blot analysis – Fluorescein isothiocyanate (FITC) Annexin V/propidium iodide (PI) apoptosis detection kit – Flow cytometry	In vitro study: higher levels of mitochondrial ROS and the mitochondrial protein Bad. Higher ER stress and markers of inflammation. Cells exposed to PS-MPs had higher protein levels of LC3 and Beclin 1. PS-MPs also had changes in phosphorylation of mitogen-activated protein kinase (MAPK) and protein kinase B (AKT)/mitogen-activated protein kinase (mTOR) signaling pathways. In vivo study: PS-MPs accumulated and the treated mice had more histopathological lesions in the kidneys and higher levels of ER stress, inflammatory markers and autophagy-related proteins in the kidneys after PS-MPs treatment	Mitochondrial dysfunction, ER stress, inflammation and autophagy; long-term PS-MPs exposure may be a risk factor for kidney health
Meng X, 2022 [15]	In vivo study: 65 mice were weighed and randomly divided into five group	PS-NPs (50 nm) and PSMPs (300 nm, 600 nm and 4 µm) and deionized water by gavage; 24 h exposure	– Laser Scanning Confocal Microscopy (LSCM) – Transmission electron microscope – Fourier transform infrared spectroscopy (FTIR)	– Kidney weight decrease – Increased level of BUN ($p < 0.01$). – Reduction in albumin – Histological change: necrosis and detachment of renal tubular epithelium, loss of brush border,	PS-NPs and PS-MPs bioaccumulated in the kidneys, and the aggregation PS-MPs exacerbated their biotoxicity; the PS-NPs and PS-MPs caused mice weight loss, increased their death rate, significantly alternated several

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				and scattered interstitial mononuclear inflammatory cell infiltrate – MPO value of the 50 nm group increased four times that of the control. – Increased SOD activity ($p < 0.01$). – Decrease in CAT activity – Increased the secretion of inflammatory factors in renal tissue (TNF-α, IL-6, IL-10 and MCP-1)	biomarkers and resulted in histological damage of the kidney; PS-NPs- and PS-MPs- induced oxidative stress and inflammation
Zou H, 2022 [20]	In vivo study: mice	Mice were treated with Cadmium (50 mg/L) and/or 5 µm MPs (10 mg/L) for 90 days	Transmission electron microscopy – Western blotting	Tubular injury – Higher MDA levels – SOD2 and Sirt3 levels significantly elevated in the co-treatment group – Autophagy marker LC3 and the early autophagy proteins ATG5, Beclin-1 and ATG7 were significantly higher	MPs exacerbated Cd-induced kidney injury. MPs aggravated Cd-induced kidney injury by enhancing oxidative stress, autophagy, apoptosis and fibrosis

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				in the co-treatment group – α-SMA and COL4A1 significantly higher in the co-treatment group – e Bax/Bcl-2 ratio was increased in the co-treatment group compared with that in the Cd group, and the expression levels of their downstream regulatory proteins, Caspase-3 and Cleaved Caspase-3, were both significantly increased	
Goodman KE, 2022 [17]	In vitro study: Human embryonic kidney 293 cells (HEK 293)	HEK 293 treated with 5 and 100 µg/mL PS-MPs	– Flow cytometry – RT-PCR analysis	– Decline in the net metabolic activity for HEK 293 cells exposed to MPs – Significant declines in cellular proliferation rates due to microplastic exposure – Increase in ROS levels over time for each concentration –	Threse morphological, metabolic, proliferative changes and cellular stress, indicate the potential undesirable effects of MPs on human health

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				HEK showed lower expression of SOD2 and CAT for 5 and 100 µg/mL exposed cells at 24 and 72 h, decrease of GAPDH at 24 and 72 h after MP exposure	
Meng X, 2022 [16]	In vivo study: 120 chicken (1-day-old randomly assigned to 4 groups.	PS-MPs (1, 10, 100 mg/L) for six weeks, with 1 mg/L	– Transmission electron microscopy – Western blot analysis – Quantitative reverse transcription polymerase chain reaction (qRT-PCR) – RNA sequencing and bioinformatics analysis	– Mitochondrial morphology and dysbiosis (MFN1/2, OPA1, Drp1), mitochondrial structural damage by triggering imbalance in mitochondrial dynamicsAntioxidant enzyme (SOD, CAT, MDA, GSH, T-AOC) activity was significantly altered, which in turn caused oxidative stress – H&E staining results showed damage and inflammation of chicken kidney by activated NF-κB P65 and increased expression of pro-inflammatory factors (TNFα, iNOs, IL-1β and IL6) –	This study was the first to show that oral intake of PS-MPs induced inflammation and necroptosis in chicken kidney and the differences in damage were linked to the concentration of PS-MPs

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				Necroptosis through activated RIP1/RIP3/MLKL signaling pathway	
Chen YC, 2022 [18]	In vitro study: human embryonic kidney 293 (HEK29)	The HEK293 cells were treated with PSMPs (3–300 ng/mL) for 24 h.	– Western blot analysis – Histology	PSMPs can: – Adhere to the cell membrane and get entirely engulfed by HEK293 cells; – Induce cytotoxicity by oxidative stress via inhibition of the antioxidant haem oxygenase-1; – Induce depolarisation of the mitochondrial membrane potential and formation of autophagosomes confirmed that apoptosis; – Activate the inflammatory factor; – induced autophagy, which might further reduce NLRP3 expression; – Impair kidney barrier integrity and increase the probability of developing acute	These results demonstrated that environmental exposure to PSMPs may lead to an increased risk of renal disease

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				kidney injury through the depletion of the zonula occludens-2 proteins and α1-antitrypsin	
Xiong XI, 2023 [21]	[21] In vivo study: C57Bl/6 J mice (3 weeks old; male)	H_2O, 80 nm, 5 µm, and 0.5 µm groups according to the diameter of MPs.	– Quantitative reverse transcription polymerase chain reaction (qRT-PCR) – Transmission electron microscopy (TEM) – RNA sequencing and bioinformatics analysis	– Inflammatory response, oxidative stress and cell apoptosis in the kidney and induce kidney injury (disrupt glomerular integrity and barrier function, and cause endothelial cell damage) which ultimately promotes kidney fibrosis; transcriptome data revealed that chronic exposure to MPs could alter the expressions of multiple genes related to immune response and circadian rhythm	These data provide new evidence and potential research for investigating the harm of MPs to kidney of mammals and even humans
Sun x, 2023 [19]	In vitro study: Human kidney embryonic cells (HEK29)	4 groups: the control, DEHP, MPs, and DEHP + MPs group – DEHP group were treated with 100 µM	– Histology – Transmission electron microscopy – Immunofluorescence	– Significantly increased expression levels of ROS/AMPK/ULK1 and Ppargc1α/Mfn2	The combined exposure to DEHP and PS-MPs caused oxidative stress and activated the AMPK/ULK1

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	– In vivo study: 60 SPF-grade Kunming mice aged 6–8 weeks	– DEHP for 24 h; – MPs group were treated with 300 μg/mL PS-MPs for 24 h – DEHP + MPs group were treated with 100 μM DEHP and 300 μg/mL PS-MPs for 24 h	– Real-time quantitative PCR, – Western blot analysis	signaling pathway-related genes; – Upregulation of the mRNA and protein expression levels of autophagy markers	pathway, thereby inducing renal autophagy

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