Will microplastics be a new cause of hepatotoxicity in the future?

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Abstract. The presence of microplastics in ecosystems is a recognized threat to wildlife and plants due to industrial plastic products and their degradation. These particles contaminate soil, water, and air, posing a threat to humans, particularly through contaminated food and water sources. Recent research has shown the presence of microplastics in human tissue, including blood, placenta, and various organs. Studies in humans have found microplastics in feces and liver tissue samples, with polypropylene and polyethylene terephthalate being the most common. Individuals with cirrhosis have had microplastics detected in their liver tissue. Studies in animals show links between microplastics and energy disruption, lipid metabolism, oxidative stress, and inflammation. Research on the accumulation of microplastics in human livers is still limited. Existing studies mostly focus on animal models, indicating potential hepatotoxic effects. These effects include alterations in hepatocyte architecture, disturbances in energy and lipid metabolism, and increased production of reactive oxygen species (ROS). Additionally, prolonged exposure to microplastics in animals has been associated with changes in enzyme function parameters. In vitro studies further demonstrated that microplastics smaller than 1μm can enter hepatocytes, leading to liver damage, dysfunction, and fibrosis. While the evidence supports the potential hepatotoxicity of microplastics, direct correlations in healthy humans are still emerging. It is crucial to continue researching this area to better understand the implications of microplastic accumulation in human tissues, particularly the liver. This knowledge will be essential for formulating strategies to mitigate potential impacts on human health and the environment.

Keywords. Microplastics, Human Tissue, Nanoplastics, Polymers, Liver.

1. Introduction

The widespread presence of microplastics (MP) in various ecosystems is already widely recognized as a serious problem, posing a serious risk to fauna and flora. These microplastics are predominantly derived from industrial plastic products or result from the degradation of these materials. Studies have shown that they contaminate not only soil, but also water (Jambeck JR, Geyer R, Wilcox C, et al. 2015) and air (Rachid Dris et al. 2016). With regard to humans, the threat is imminent since the entry of these particles into the body occurs mainly through the ingestion of contaminated food, especially from marine animals (Van Cauwenberghe et al. 2012), as well as through the consumption of contaminated water, honey, and sugar (Liebezeit et al. 2013) Furthermore, contamination can occur via air and skin (Laura M et al. 2017).

Although the presence of these microplastics in the environment and their influence on the contamination of fauna, mainly aquatic (Wright et al. 2013), have been known and studied for a long time, it was only after 2020 that research and results began to emerge that demonstrate the presence and accumulation of these particles in human tissues. Initially, the presence of microplastics was identified in the blood and feces of human beings, followed by detection in the placenta, as well as in fetal and neonatal blood (Heather et al. 2022, Ragusa et al. 2022, Schwabl et al. 2019). These particles were later found in the intestinal mucosa, liver, kidneys, spleen, heart and lungs of humans, sometimes in lower concentrations or associated with chronic diseases. (Lauren C. Jenner et al. 2022, Ibrahim et al. 2020, Horvatits et al. 2022, Yang et al. 2023).

Furthermore, due to long-standing research into the presence of these microplastics in animals, several studies have investigated the repercussions of the presence of these particles in mammalian tissues, revealing a direct correlation with energy disorders, lipid metabolism, oxidative stress and pro-

inflammatory reactions (Martínez-Álvarez et al. 2005, Babaei et al. 2022). The accumulation of these microplastics and their consequences for human physiology have been studied recently, and it is still necessary to clarify more precisely how the accumulation pattern occurs in each organ, what the main possible consequences are, and whether the presence of these particles in human organs, like the brain, is just a matter of time. Fully understanding these effects is crucial for formulating effective strategies to mitigate and prevent the impacts of microplastics on human health and the environment as a whole. Generally, larger microparticles are prone to being expelled through feces or eliminated via mucociliary clearance after they have been deposited in the lungs (Yang et al., 2022).

Upon ingestion, the size of microplastics directly influences their absorption. Microplastics are defined as plastics smaller than 5mm (Ragusa et al., 2022), but there are also nanoplastics (NP), which are smaller than 1µm (Dawson et al., 2018). Some microplastics are too large to enter the intestinal mucosa from the lumen and are therefore found in feces, but microplastics smaller than 150µm can cross the gastrointestinal epithelium (Powell et al. 2020), where they can accumulate in the gut or cross the capillary endothelium and find systemic circulation; particles smaller than 2.5µm can cross the endothelium by endocytosis (Coméra et al. 2020). Through portal circulation, microplastics immediately pass through the liver, where they can accumulate.

There is still a lack of studies addressing the presence of microplastics in the human liver. However, there are several studies already showing its detection and accumulation in the liver tissue of marine animals, such as zebra fish (Lu Y, Zhang Y, Deng Y, et al. 2016) and crustaceans (Araújo APDC, Gomes AR et al. 2020), as well as some toxic effects in the tissue of these animals and in mammalian cells, such as rodents (Martínez-Álvarez et al. 2005, Babaei et al. 2022). The proposal is that by inducing the accumulation of microplastics in the tissue of these animals, it will be possible to identify patterns of injury, and, in the future, it will be possible to identify these same patterns in human tissue if human livers with an accumulation of microplastics are found. However, this accumulation of microplastics in human livers has not yet been very well documented, and although it exists, there is still a lack of samples that can directly work with the effects of MPs in human tissue.

2. Methods

The selection of articles for this literature review was carried out using Google Scholar and PubMed using the keywords: “Microplastics”, “Nanoplastics”, “Human tissue”, “liver”, “human liver”, “hepatic”. Duplications were excluded, and synonyms of the keywords were used. The articles most relevant to the search were selected, and from their references, other articles were selected that completed the research on the topic, whose main keywords were “oxidative stress” and “lipid metabolism”.

3. Results

(Araújo APDC, Gomes AR et al. 2020) tested the hypothesis that exposing Physalaemus cuvieri tadpoles to microplastic polyethylene (PE MP) leads to histopathological damage in their liver. Data were gathered after seven days of exposure to MPs at a concentration of 60 mg/L. The histopathological alterations included blood vessel dilation, infiltration, congestion, hydropic degeneration, hypertrophy, and hyperplasia. These changes highlight the histopathotoxicity of MPs. It was also observed that alterations in hepatocyte nuclei size, volume, and shape occurred as a result of exposure to PE MPs, indicating the cytotoxic effects of these pollutants.

A study done on Zebrafish detected the accumulation of polystyrene microplastics, and within 7 days after exposure, 5 µm diameter MPs accumulated in fish gills, liver, and gut, while 20 µm diameter MPs accumulated only in fish gills and gut. The two sizes of MPs caused inflammation and lipid accumulation in the fish, as well as increased activity of superoxide dismutase and catalase, indicating oxidative stress caused by the presence of MPs. Exposure to MPs also altered the metabolic profile of the fish, disturbing energy and lipid metabolism (Deng Y, Zhang Y et al. 2017).

In mammals, prolonged exposure to microplastics was tested in Wistar rats. The animals received oral doses of polystyrene nanoplastics for 5 weeks at different doses. The result showed the accumulation of these NPs, as well as the dose-equivalent increase in the production of reactive oxygen species (ROS). Excessive ROS can damage lipids in cells and lead to lipid peroxidation (LPO) (Martínez-Álvarez et al. 2005) There were changes in the antioxidant responses of rodents, with an increase in catalase. Hepatic enzyme function parameters such as cortisol, lipase, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), triglycerides, and urea showed a significant increase, while total protein, albumin, and globulin levels showed an appreciable decline. As in zebrafish, the pattern of changes in energy and lipid metabolism was maintained in rodents (Babaei et al. 2022).

(Deng et al.) Also studied the pattern of accumulation and distribution of MPs in rats, reaching a similar conclusion regarding their accumulation in the liver, kidneys and intestine. Again, biochemical biomarkers consistent with disturbances in energy and lipid metabolism in rodents, as well as oxidative stress, were reported. Blood biomarkers of neurotoxicity have also been reported to be present.

The hepatotoxic profile has been reported in other studies with mices (Lu L, Wan Z, Luo T, Fu Z, Jin Y. et al. 2018), (Yang Y-F, Chen C-Y, Lu T-H, Liao C-M. et al

2019). It was also shown that exposure of these mice to microplastics decreased the mRNA levels of important genes involved in lipogenesis and triglyceride synthesis in their livers. Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. Jin Y, Lu L et al. (2019) reported changes in transcriptional levels of CYP7a1 and ABCb11, two proteins involved in bile acid synthesis and transport in the livers of mice exposed to 5μm MPs.

In humans, eight healthy volunteers had their feces tested for microplastics, all 8 stool samples tested positive for microplastics. A median of 20 microplastics (50 to 500 μm in size) per 10 g of human stool were identified. Overall, 9 plastic types were detected, with polypropylene and polyethylene terephthalate being the most abundant. Still in the gastrointestinal tract, Colectomy samples were obtained from 11 adults (mean age 45.7, six males) who were residents of Northeastern Peninsular Malaysia. Analysis was done, and Microplastics were identified following chemical digestion of the specimens and subsequent filtration. Microplastics were detected in all 11 specimens with an average of 331 particles/individual specimen, or 28.1 ± 15.4 particles/g tissue. (Ibrahim YS, Tuan Anuar S, Azmi AA, et al. 2020).

Horvatits T, Tamminga M, Liu B, et al, (2022) analyzed tissue samples from six patients with liver cirrhosis and five individuals without underlying liver disease. A total of 17 samples (11 liver, 3 kidneys and 3 spleen samples) were analyzed according to the final protocol. This proof-of-concept case series assessed the presence of MPs in human liver tissue and found six different MP polymers in the liver of individuals with liver cirrhosis but not in those without underlying liver disease. The author also raises the possibility that cirrhosis is related to the accumulation of microplastics in the liver, but that it is more likely than the cirrhotic condition that it would lead to greater ease of accumulation of microplastics.

Shen R, Yang K, Cheng X, et al. (2022) demonstrated by in vitro studies that microplastics smaller than 1 μm can enter hepatocytes and deposit in the liver through circulation. Long-term accumulation of these MPs induced liver damage and liver dysfunction. Micro-PS leads to nuclear DNA and mtDNA damage, subsequent activation of the cGAS/STING signaling pathway is involved in mediating liver fibrosis. The initiation of the cGAS/STING pathway triggered a subsequent cascade of events. This led to the translocation of NFκB into the nucleus, resulting in the up regulation of pro-inflammatory cytokine expression, ultimately promoting the progression of liver fibrosis.

Using a 3D in vitro model of a human liver, formed from pluripotent stem cells, the consequences of exposure to 1 μm polystyrene-MP were tested again. Similar results were found: hepatotoxicity due to changes in energy and lipid metabolism. Cytotoxicity by MPs was marked by molecular markers, ATP production, ROS production, oxidative stress and an inflammatory response, again associating the findings with the identification of future risks to human health since studies demonstrate a potential relationship between MPs and steatosis and liver fibrosis. (Cheng W, Li X, Zhou Y, et al. 2021).

4. Discussion

Through this systematic review, we concluded that it is too early to associate the accumulation of microplastics in human liver tissue with a future cause of hepatotoxicity. The studies and references discussed, as well as other studies carried out but not cited, in fact provide strong results regarding the capacity for accumulation of MPS in animal tissue and its hepatotoxic role in marine animals and rodents, just as in vitro studies can demonstrate cellular injuries. However, the lack of studies demonstrating the accumulation of microplastics in healthy humans and directly showing MP-mediated hepatotoxicity in real livers does not allow for a solid correlation between microplastics and liver injury in humans.

With a literature review, we understand that in vitro studies and studies on marine animals and mammals have demonstrated the ability of microplastics to enter the human body mainly through ingestion. Microplastics and nanoplastics can accumulate in tissues, mainly the blood, placenta, intestine, kidneys and liver. Studies with prolonged exposure to microplastics in animals have demonstrated their accumulation and a potential cytotoxic effect on the tissues in which they accumulate. In the liver, the accumulation of MPs was directly related to disturbances in energy and lipid metabolism, with increased production of reactive oxygen species (ROS), damage to hepatocyte architecture, and increased catalase. Disturbances in lipogenesis and triglyceride synthesis, as well as long-term liver damage and dysfunction, have also been shown. Thus, the accumulation of microplastics can possibly be related to steatosis and liver fibrosis.

5. Conclusion

Studies demonstrate the increasing detection of microplastics in animal tissues as well as their accumulation. The possible cytotoxic action of microplastics is being continuously studied, seeking to predict future damage caused by the accumulation of MPs in human tissue. The liver is a possible organ to be targeted in the future, given the ability of MPs to accumulate in the livers of fish and mammals and cause hepatotoxicity. For now, the studies are too recent to conclude a direct correlation with hepatotoxicity in healthy humans, but we need to maintain this line of research so that, in the future, we are not surprised by microplastics being a new cause of liver damage.

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