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Original Article

Low-Density Polyethylene Microplastics in Blood Does Not Increase Serum Aß1-42 Levels as a Biomarker of Alzheimer's Disease in Wistar rats

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Abstract

Introduction: The presence of microplastics in the blood circulation will trigger the formation of free radicals as a cause of damage to brain neurons. The large number of dead neuron causes a decrease in cognitive function which is the pathological of Alzheimer's disease. Amyloid beta 1-42 (Aβ1-42) levels in blood serum was a biomarker of Alzheimer's disease. This study aim was to explain the effect of microplastic particles in the blood toward the accumulation of Aβ1-42 levels in blood serum. Materials and methods: This study was a purely experimental study with post-test group design by using 42 Wistar rats which were divided equally into six groups. The control group was no exposed to microplastics, study group 1 (X1) was given 0.0375 mg/days, 2 (X2) was given 0.075 mg/day, 3 (X3) was given 0.15 mg/day, 4 (X4) was given 0.3 mg/day, and 5 (X5) was given 0.6 mg/day. Microplastics dry powder <20 μm in size mixed with 2 cc of distilled water and given through a probe for 90 days. Result: Microplastic particles have been found in the blood of Wistar rats, which were in higher number along with the group exposed to high doses of microplastics. There was an increase in Aβ1-42 levels in blood serum in the study group exposed to small doses, whereas decreased in the study group exposed to larger doses. Statistical analysis between two variables using by Spearmen's rho test showed p value >0.05. Conclusions: There was no evidence that microplastic particles in the blood lead to increase Aβ1-42 levels in blood serum to assess cognitive abilities in Alzheimer's disease. It is concluded that microplastic particles in the blood does not induce Alzheimer's disease in Wistar rats.

Keywords: Alzheimer's disease, amyloid beta 1-42, environmental pollution, microplastics, Wistar rats.

Introduction

Microplastics (plastic particles <5 mm) pose health problems to humans. One of the entry points for microplastics in humans was through consumption of contaminated food. Microplastic consumption per day in adults was 126-142 MP and children was 106-113 plastic particles [1]. These plastic particles are found in table salt, canned sardines, beer, sea fish, honey, sugar, tea bags, minerals and drinking water [2–6]. These findings estimated between 37 to as high as billion plastic particles from various food products [7].

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The number of plastic particles that contaminate food and beverages will continue to increase along with the increase in plastic debris in the environment [8].

Microplastics in the digestive tract will be phagocytosed into the blood and lymph circulation [9]. These particles will try to be destroyed by cellular defense mechanisms [10], through both oxygen-dependent and oxygen-independent mechanisms [11]. Furthermore, microplastics will circulate to all parts of the body. These particles have been reported in the liver, lungs, heart, muscles, kidneys and brain [9,10,12–15]. Some microplastic particles will be excreted with the feces [16,17]. The most widely identified plastic polymer in human faeces is polyethylene [17].

Microplastics in the body will trigger oxidative stress due to high free radicals [10,14]. A decrease in antioxidant enzymes was seen in studies using microplastics as an exposure material [3,12–14]. Free radicals induced by microplastics come from three components, namely plastic monomers, endogenous additives included during the production process (such as phthalate, bisphenol A, nonylphenol, polybrominated diphenyl ethers) and environmental pollutants absorbed while in nature (such as polychlorinated biphenyls; polycyclic aromatic hydrocarbons; 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane, 1,1dichloro-2,2 bis (chlorophenyl) ethylene, and heavy metals) [3,9,18]. These various toxic compounds also enter the body along with the entry of microplastics.

Disruption of the cell barrier due to reactive oxygen species (ROS) will initiate cell damage and death [19,20]. Damage due to ROS also occurs in brain neurons [21]. If neuronal damage occurs continuously, it causes the remaining cells to be unable to maintain the normal function of the brain organs. This condition was known as the pathophysiology of Alzheimer's Disease [22]. Cognitive function impairment occurs due to the number of damaged brain neurons [23]. Microplastics have been known to trigger neuronal damage, but whether these pollutants cause Alzheimer's disease remains to be investigated. In theory, the toxicity of microplastics requires the accumulation of a certain dose and time to cause an effect other than the influence of particle size [9,10,20].

Amyloid beta 1-42 (Aβ1-42) was used as a marker to assess cognitive abilities in Alzheimer's disease [24,25]. Aβ1-42 protein was derived from the fragmentation of amyloid precursor protein (APP). APP plays a role in the growth, survival, and repair of damaged brain neurons [26]. Increased accumulation of Aβ1-42 protein in blood serum indicates that there has been damage to neurons in the brain. Furthermore, this protein will undergo fibrillation to become amyloid plaque in brain neurons. This causes a decrease in the accumulation of Aβ1-42 in the blood serum [21,25]. The large number of amyloid plaques or the low accumulation of Aβ1-42 in the blood serum indicates that there has been a decrease in cognitive abilities. This condition indicates Alzheimer's disease has occurred [21,22,25]. High levels of ROS in the body will increase the amount of amyloid plaque deposits in the brain which significantly reduces cognitive abilities due to the death of brain neurons [25]. Amyloid plaques will bind to the ends of dendrites so that impulses cannot be received by dendrites, synapses no longer function for signal transmission. In addition, the accumulation of Aβ1-42 in blood serum also reduces synapse plasticity [27]. These various conditions initiate the death of brain neurons.

Therefore, the aim of this study was to analyze influence the blood low-density polyethylene microplastics toward to the accumulation of Aβ1-42 in blood serum as an indication of cognitive impairment in Alzheimer's disease.

MATERIALS AND METHODS

Experimental animals

Wistar rats was used as experimental animal. Male rats, healthy, nine weeks old, weighing 140-170 grams were purchased from the Farma Veterinary Center in Surabaya. Rats were put in 40x60x20cm cages, given husks and covered with wire. Drink water from a water bottle and eat PUR 594 ad libitum. The rat care environment was cleaned every morning, air circulation was stable, room temperature was 18-26°C, and humidity was 40-70%.

Research design

Pure experimental study, with post-test only randomized experimental design. Using 42 Wistar rats which were divided equally into six groups based on the Lemeshow formula (α =0.05 and β =0.05), namely one control group (C) and five study groups (Xn). Group C was not given microplastics. The study groups X1, X2, X3, X4, X5 were given microplastic particles of 0.0375mg, 0.075mg, 0.15mg, 0.3mg, 0.6mg, respectively. At the end of the exposure period, Wistar rats were anesthetized using injection of ketamine-xylazine and 2 cc of blood was drawn through the heart. After that, Wistar rats were euthanized by cervical dislocation technique. The rest of the rats were put in a wooden box and cremated so as not to pollute the environment. The research was carried out at Widya Mandala Surabaya Catholic University from October 2021 to March 2022. One cc of blood sample in vacutainers was taken to Balai Besar Laboratorium Kesehatan in Surabaya using a cooler box to assess serum levels of amyloid beta 1-42 (Aβ1-42), while another cc of blood was immediately assessed for the levels of microplastic particles in the blood.

Exposure material

The microplastics used come from plastic bags (low-density polyethylene). This plastic was fragmented using a Miller FCT-Z100 (Fomac, Indonesia) to the size of a microplastic into a fine powder. The plastic powder was filtered using sieve number 800 mesh (Anping Tianhao Wire Mesh Products Co., Ltd, China). After that, it was examined with a Nikon eclipse Ci-L-DS-F12-L3 microscope binoculars

(magnification 400 and 10 μm scale) to ensure the particle size was <20 μm (Figure 1). The plastic powder was weighed according to the dosage and mixed 2 cc of distilled water and shaken until it was mixed into a suspension solution. This solution was given to each Wistar rat for 90 days using an oral probe.

Examination of microplastic particle levels in blood

The procedure for examining blood microplastic particles was carried out by destruction of blood using a solution of KOH-10% and HNO_3-67%, isolation of microplastic particles by centrifugation and sonification, then filtration using S-PAK membrane filter 0.45μm Millipore® mix cellulose sterile white gridded 47mm. This procedure has been used and previously described by Monteleone et al. The quantification of the microplastic particles in blood was using a light microscope in five fields of view. This procedure was performed by a clinical pathologist.

Examination of amyloid beta 1-42 levels in blood serum

Examination of amyloid beta 1-42 (Aβ1-42) levels in blood serum rats by Sandwich-ELISA following the Rat Aβ1-42 ELISA Kit protocol (Elabscience Biotechnology Inc® USA). Rat whole blood samples in plain vacutainer were left for 24 hours at 8°C. After that, the samples were centrifuged for 20 minutes at 1000×g. The supernatant from the centrifugation was tested. The next process follows the factory procedure and has been used by Aizuddin on his research. In the right procedure, the Aβ1-42 protein complex will fluoresce so that the levels of Aβ1-42 in the rat blood serum can be calculated [28]. The examination procedure was carried out by a clinical pathologist.

Statistical test

Statistical analysis of the results in this study was performed using SPSS for Windows version 18.0. Analyzes were performed at least three times independently. Each of research results were shown in table and figures. The results are expressed as the mean ± standard deviation (SD). Normality test using Shapiro-wilk, obtained p value <0.05, which means that the microplastic particle and amyloid beta 1-42 variables have an abnormal distribution. Spearman's rho test was used because the normality of the data was not met. Significant if the p value < 0.05 at the 95% confidence interval, while the correlation coefficient to determine the direction and strength of the relationship between variables.

Ethics statement

This study followed the ethical principles and received an ethics certificate (reference number 209/WM12/KEPK/DOSEN/T/2021) from the Health Research Ethics Committee of Widya Mandala Surabaya Catholic University.

RESULTS

Microplastic particle levels in blood

Figure 2 shows that the control group (C) which was not exposed to microplastics also found microplastic particles in the blood which indicated contamination. The number of microplastic particles in the blood of Wistar rats was higher along with the group exposed to high doses of microplastics. There was significant increase in the number of microplastic particles in the study group given an exposure dose of 0.15 mg per day (study group X3). The mean microplastic particles in the study groups X3, X4, and X5 were almost the same.

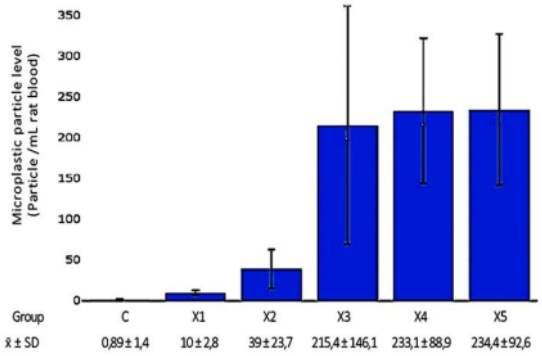

Figure 1 : Mean levels of microplastic particles in the blood of Wistar rats

Description: C= control group or without exposure microplastic; X1= exposed to 0,0375 mg microplastic; X2= exposed to 0,075 mg microplastic; X3= exposed to 0,15 mg microplastic; X4= exposed to 0,3 mg microplastic; X5= exposed to 0,6 mg microplastic.

Amyloid beta 1-42 levels in blood serum

Figure 3 shows that the mean amyloid beta 1-42 (Aβ1-42) in blood serum of Wistar rats in all groups exposed to microplastics (study group X1, X2, X3, X4, X5) was lower than the control group (C). The control group was the normal reference value for Aβ1-42 levels in rat blood serum, which is 4.60 ± 0.76. There was an increase in Aβ1-42 levels in the study group exposed to small doses, then decreased in the study group exposed to larger doses. The lowest mean was found in the group exposed to 0.6 mg of microplastics per day (study group X5).

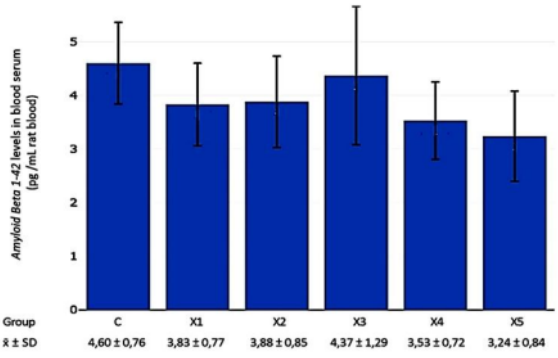

Figure 2: Mean levels of amyloid beta 1-42 in the blood

serum of Wistar rats

Description: C= control group or without exposure microplastic; X1= exposed to 0,0375 mg microplastic; X2= exposed to 0,075 mg microplastic; X3= exposed to 0,15 mg microplastic; X4= exposed to 0,3 mg microplastic; X5= exposed to 0,6 mg microplastic.

Correlation analysis between blood levels of microplastic particles and blood serum amyloid beta 1-42 levels

Statistical analysis using the Spearmen's rho method obtained a p value > 0.05, which means that there was no significant correlation between microplastic levels in the blood and levels of amyloid beta 1-42 in the blood serum of Wistar rats (Table 1). The strength of the correlation was also weak with negative direction. This means that the more microplastic particles in the blood does not significant cause decrease in amyloid beta 1-42 in blood serum, although this decrease still occurs.

Tabel 1: Spearman's rho analysis between blood levels of microplastic particles and blood serum amyloid beta 1-42 levels

Parameter	Value
Correlation Coefficient	- .289
Asymptotic significance (2-tailed)	.060
Explanation	Not Significant

DISCUSSIONS

The low-density polyethylene used in this study was <20 μm in size, solid particles with rough edges. Solid particles and rough edges may play a role in the pathophysiology of microplastic toxicity. This makes the microplastic particles unable to be destroyed by the body's defense mechanisms. Attempts to destroy these foreign bodies continue to trigger inflammation and reactive oxygen species [10,11]. Apart from the size and polymer of the plastic, the toxic compounds contained also determine the toxicity of microplastics to the body [29].

Microplastic exposure dose as a determinant of the number of microplastic particles in the blood of Wistar rats. The findings of this study show that the number of microplastic particles in the blood of Wistar rats was higher along with the group exposed to high doses of microplastics (Figure 1). This finding was consistent with the theory that microplastic particles containing toxic compounds in the digestive tract will be distributed into the blood circulation [9,20]. On oral intake of microplastics, the dose that significantly increased the number of microplastic particles in the blood was 0.15 mg/day. This finding was in accordance with Li study which stated that a sufficient dose to cause damage to the biological cells of Wistar rats was 5 mg of microplastic particles/L of water for 90 days (approximately 7.18×1010 particles/L) or the equivalent of 0.15 mg particles/day [12].

In this study, extrapolating an effective dose of 0.15 mg microplastic particles/day in Wistar rats to humans weighing ±70 kg was equivalent to 6.8 mg of microplastic particles/day. There is no research data that mentions microplastic contamination in human food and drink at more than this dose. This means that microplastics ingested by humans can still be compensated for by cellular defenses. This statement still needs further proof, because the results of human studies may be different from studies using animals. Nevertheless, the presence of microplastic particles in the blood can be used as a biomarker of microplastic exposure in studies using similar materials.

Microplastic particles in the blood circulation will be distributed to all organ tissues [9,10,20]. In the brain, microplastic particles trigger neuronal injury by oxidative stress and inflammation [30]. In addition, exposure to microplastics can inhibit acetylcholinesterase activity and alter neurotransmitter levels. Microplastics cause neuronal damage and increased neurological disorders [30–32]. Amyloid Precursor Protein (APP) will play a role in the repair of damaged neurons. These repair efforts lead to fragmented APP [26]. APP fragmentation by beta-secretase enzymes will increase the accumulation of amyloid beta protein in blood [21,26]. The findings of this study are consistent with the statement above, namely that there was an increase in Aβ1-42 levels in the study group exposed to small doses of microplastic, then decreased in the study group exposed to larger doses (Figure 2). The decrease occurs because Aβ1-42 in blood serum undergoes fibrillation to become amyloid plaque in brain neurons [25]. Amyloid plaques will disrupt Ca2+ homeostasis in neurons, thereby making neurons more easily damaged by free radicals from microplastics. In addition, amyloid plaques make dendrites unable to receive impulses. Furthermore, neurons that have lost the ability to communicate will die [22,25,27]. This condition was the pathophysiology of Alzheimer's disease. The number of dead neurons will cause the synthesis of APP to decrease so that the amount of Aβ1-42 accumulation in the blood serum will also decrease.

Based on statistical analysis (Table 1), the more microplastic particles in the blood does not directly cause a decrease in the levels of amyloid beta 1-42 in the blood serum. Even so, the data in this study showed that the impact of decreasing beta amyloid levels occurred in the group that had the most microplastic particles in the blood, whereas in microplastic particles in the blood as many as 10 to 215 particles (equivalent to an exposure dose of 0.0375 mg/days to 0.15 mg/days) can be repaired by the role of amyloid precursor protein as seen from the increase in Aβ1-42 in blood serum.

There are three limitations in this study. First, the variation in the exposure dose used was too small to be statistically significant. Decreased Aβ1-42 levels were seen only at doses of 0.3 mg/day and 0.6 mg/day. Second, it does not measure amyloid plaque in brain neurons. Third, this study

also did not examine other chemical compounds contained in microplastic particles. As our recommendation, our three limitations need to be considered in similar studies. Statistical analysis could be significant at larger doses and longer duration of exposure.

CONCLUSION

There was no evidence that microplastic particles in the blood lead to increase amyloid beta 1-42 (Aβ1-42) levels in blood serum to assess cognitive abilities in Alzheimer's disease. It is concluded that microplastic particles in the blood does not induce Alzheimer's disease in Wistar rats.

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