Biological Trace Element Research (2022) 200:1591–1597
https://doi.org/10.1007/s12011-021-02766-3

Harmful Effects of Inorganic Mercury Exposure on Kidney Cells: Mitochondrial Dynamics Disorder and Excessive Oxidative Stress

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Received: 3 May 2021 / Accepted: 24 May 2021 / Published online: 31 May 2021
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Abstract

Mercury is widely used in industry and has caused global environmental pollution. Inorganic mercury accumulates in the body causes damage to many organs, and the kidney is the most susceptible to the toxic effects of mercury. However, the underlying specific molecular mechanism of renal injury induced by inorganic mercury remains unclear at the cellular level. Therefore, in order to understand its molecular mechanism, we used *in vitro* method. We established experimental models by treating human embryonic kidney epithelial cell line (HEK-293 T) cells with $HgCl_2$ (0, 1.25, 5, and 20 μmol/L). We found that $HgCl_2$ can lead to a decrease in cell viability and oxidative stress of HEK-293 T, which may be mediated by upregulation mitochondrial fission. In addition, $HgCl_2$ exposure resulted in the mitochondrial disorder of HEK-293 T cells, which was mediated by downregulating the expression of silent information regulator two ortholog 1 (Sirt1)/peroxisome proliferator–activated receptor coactivator-1α (PGC-1α) signaling pathway. In summary, our results suggest that $HgCl_2$ induces HEK-293 T cell toxicity through promoting Sirt1/PGC-1α axis-mediated mitochondrial dynamics disorder and oxidative stress. Sirt1/PGC-1α may be an appealing pharmaceutical target curing $HgCl_2$-induced kidney injury.

Keywords $HgCl_2$ · Mitochondrial dynamics dysfunction · Sirt1/PGC-1α · ROS · Kidney cell

Abbreviations

$HgCl_2$	Mercury dichloride
HEK-293T	Human embryonic kidney epithelial cell line
PGC-1α	Peroxisome proliferator-activated receptor coactivator-1α
Sirt1	Silent information regulator two ortholog 1
Mfn1	Mitofusin 1
Mfn2	Mitofusin 2
Drp1	Dynamin-related protein 1
ROS	Reactive oxygen species
ATP	Adenosine-triphosphate
qRT-PCR	Quantitative real-time PCR

Introduction

Mercury is a heavy metal toxic substance that exists in the environment for a long time and has global mobility. Mercury pollution comes from a wide range of sources, such as polyvinyl chloride resin, medical products, batteries, and other manufacturing industries [1]. Acute and chronic mercury poisoning caused by many causes can damage various organs such as the skin, pulmonary, neurological systems, and urinary [2]. In 2010, there were 7360 deaths from heart disease due to mercury exposure on the Chinese mainland [3]. With the pollution aggravation of mercury, its potential toxicity in humans and animals has gradually risen.

Mercury exists in the environment in the form of elemental, organic, and inorganic compounds. Inorganic mercury tends to accumulate in the kidney, leading to renal failure [4, 5]. The absorption and accumulation of mercury in the kidneys is very rapid, and up to 50% of low-dose inorganic mercury exposure (0.5 μmol kg^{-1}) was found in the kidney

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of rats in a few hours [6]. Research has shown that mercury chloride ($HgCl_2$) treatment may cause necrosis and apoptosis of renal tubules, destroy the structure of renal tubules, and thereby affect renal function [7]. Nevertheless, the exact mechanism of nephrotoxicity caused by inorganic mercury is still unclear.

The kidney is a highly metabolized organ that requires ample adenosine triphosphate for active transport, and mitochondria play an essential role in energy production. Thus, the content of mitochondria in the kidney is second highest only to the heart [8]. Mitochondrial fusion is regulated by mitofusins 1 and 2 (Mfn1 and Mfn2), and dynamin-related protein 1 (Drp1) participates a vital link in mitochondrial fission. The fusion and fission of mitochondria are responsible for regulating their morphology and number, and the two generally in a state of dynamic balance [9]. Nevertheless, quite a few poisons will break this balance, and the period tends to be mitochondrial fission, which results in apoptosis under oxidative stress [10, 11]. Hence, additional research is needed to investigate whether the disruption of mitochondrial dynamics is the key of renal injury caused by inorganic mercury.

Peroxisome proliferator–activated receptor-γ coactivator (PGC-1α) mediates mitochondrial biogenesis and is an essential regulator of energy homeostasis [11, 12]. Sirtuin 1 (Sirt1) regulates the cell cycle, apoptosis, inflammation, oxidative stress, and other processes of cells. It is determined that PGC-1α is deacetylated and activated by Sirt1. Thus, the Sirt1/PGC-1α axis may be a key target of kidney injury.

The damage of renal epithelial cells is closely related to nephropathy, and its damage will cause the decline of renal function [13]. In this study, we treated the human embryonic kidney epithelial cell line (HEK-293 T) with different concentrations of $HgCl_2$ (1.25, 5, and 20 μmol/L) for 24 h, respectively. Then, we examined the effect of inorganic mercury on cell viability, reactive oxygen species (ROS), and some representative mRNA and protein levels (Drp1, Mfn2, PGC-1α, and Sirt1). Our current work aimed to discuss the role of inorganic mercury in kidney injury from the perspective of mitochondrial dynamics.

Materials and Methods

Materials

Mercury ($HgCl_2$, Beijing Chemical Works, China) was dissolved in double-distilled water, sterilized with filters. Cell Counting Kit-8 (CCK-8) and ROS detection were acquired from Beyotime Biotechnology (Shanghai, China). Dulbecco's Modified Eagle's Medium (DMEM) was obtained from Meilun Biotechnology Co., Ltd (Dalian, China). TRIzol reagent was the product of Invitrogen (Carlsbad, CA, USA), and penicillin-streptomycin was purchased from Leagene Biotechnology (Beijing, China). DNA markers were supplied by GenStar (Beijing, China), and 5 × All-In-One RT MasterMix was obtained from Applied Biological Materials (abm) Inc. (Richmond, BC, Canada). Antibodies to Mfn2, Drp1, Sirt1, and PGC-1α were purchased from Beijing Biosynthesis Biotechnology (Beijing, China). The antibody to GAPDH was the product of Hangzhou Goodhere Biotechnology (China).

Cell Culture

HEK-293 T cells were obtained from the Institute of Biochemistry and Cell Biology (Shanghai, China) were cultured in DMEM containing 10% fetal bovine serum. The cells were at 37 °C in a saturated humid environment with 5% CO_2 [14].

Cell Viability Assay

First, HEK-293 T cells were seeded into 96-well microplates at a density of 1.0×10^4 cells per well. After being attached to the plates, the cells were cultured with $HgCl_2$ at various concentrations, including 0, 1.25, 5, and 20 μmol/L at the indicated time. $HgCl_2$ was dissolved with phosphate balanced solution. The previous studies provided us with reference doses for kidney cell [15]. After treatment, 10 μL CCK-8 kit reagent was contained for 4 h. Finally, the plate reader (Molecular Devices, Shanghai, China) was used to measure the solution's absorbance values at 450/630 nm [16]. The optical density represented the relative value of cell viability.

ROS Production Assay

DCFH-DA fluorescent dye assay kit was used to perform ROS level test. A total of 5.0×10^4 HEK-293 T cells per well were cultured in 6-well plates and then cultured with $HgCl_2$ (0, 1.25, 5, and 20 μmol/L). Then 10 μM ROS assay reagent was added in serum-free medium for an additional 20 min. Fluorescence intensity was measured using a plate reader (Molecular Devices, Shanghai, China) to measure 488 nm and an emission wavelength of 525 nm [17].

Quantitative Real-Time PCR

After incubation, HEK-293 T cells were collected. The total RNA was isolated from cells using the Trizol reagent as described by a previous study [16, 18]. Total RNA was used to synthesize cDNA by reverse transcription of high capacity cDNA [19, 20]. Then, the mRNA expression levels of mitochondrial dynamics-related genes, including Drp1, Mfn2, Sirt1, and PGC-1α, were assessed using quantitative real-time PCR (qRT-PCR) [21, 22]. Specific primers were

synthesized by Sangon Biotech (Shanghai, China), as shown in Table 1, the results were calculated using the standard $2^{-\Delta\Delta Ct}$ method.

Western Blot Analysis

After cells were lysed with RIPA buffer with PMSF, the protein was extracted from HEK-293 T cells, in which the BCA kit was measured the protein concentrations [23–25]. Then, the total protein was separated to 12% SDS-poly acrylamide gel electrophoresis, and we transferred it onto a PVDF membrane [26, 27]. The membranes were sealed in containing 5% skimmed milk powder and, in turn, bound with non-specific antibodies for 2 h, followed by overnight incubation at 4℃ with specific antibody the appropriately dilluted [28, 29]. Ultimately, we used Image Pro-Plus 6.0 software to perform densitometry.

Statistical Analysis

The data analysis was completed by SPSS version 19 (IL, USA). Mean ± standard error of the mean (SEM) was used to represent the results. Multiple groups were compared by analysis by one-way ANOVA following T-test, and *P* values less than 0.05 indicated significant difference.

Results

$HgCl_2$ Treatment Affected the Cell Viability of HEK-293 T Cells

To test the effect of $HgCl_2$ *in vitro*, we treated HEK-293 T cells with different concentrations of $HgCl_2$. A cell model of $HgCl_2$-induced HEK-293 T injury was established to clarify different concentrations of $HgCl_2$ to test the cell viability. We found that cell viability was significantly reduced (Fig. 1) in the $HgCl_2$-treated group (except low dosage group) compared to the control group ($P < 0.05$), which indicates the cytotoxicity of $HgCl_2$ to HEK-293 T.

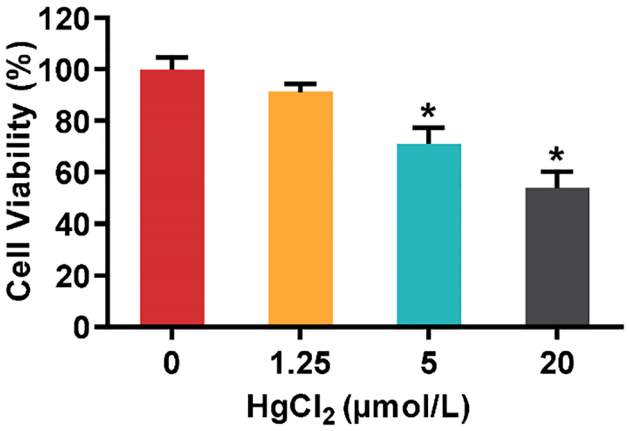

Fig. 1 Cell viability was determined by CCK-8 assay. After exposure to $HgCl_2$, a dose-dependent decrease in cell viability was observed. Data were presented as the means ± SEM, n = 6. * Meaning a significant difference ($P < 0.05$) vs control group (dosage of 0 group)

$HgCl_2$ Treatment Increased ROS Levels in HEK-293 T Cells

The level of ROS activity in HEK-293 T is displayed in Fig. 2. ROS levels increased in the middle and high group compared with the control group ($P < 0.05$, Fig. 2), which indicates the oxidative stress of HEK-293 T cells induced by $HgCl_2$.

$HgCl_2$ Affected the Expression of Mitochondria Dynamics Relative mRNA in HEK-293 T Cells

–To further investigate $HgCl_2$ treatment's effect on mitochondria dynamics, we measured the mRNA expressions (Fig. 3A–D) showed that $HgCl_2$-treated HEK-293 T cells contained significantly higher mRNA expression levels of the Drp1. Mfn2, PGC-1α, and Sirt1 mRNA expression in $HgCl_2$-treated HEK-293 T cells significantly decreased *P* values less than 0.05, except for the low-dose $HgCl_2$ group.

Table 1 Primers sequences for qRT-PCR

Gene	Genebank number	Primer sequence (5' → 3')
Sirt1	NM_001159589.2	Forward: CGCTGTGGCAGATTGTTATTAA Reverse: TTGATCTGAAGTCAGGAATCCC
PGC-1α	XM_017320718.1	Forward: GGATATACTTTACGCAGGTCGA Reverse: CGTCTGAGTTGGTATCTAGGTC
Mfn2	NM_001355590.1	Forward: GCATTCTTGTGGTCGGAGGAGTG Reverse: TGGTCCAGGTCAGTCGCTCATAG
Drp1	NM_001360010.1	Forward: ACTGATTCAATCCGTGATGAGT Reverse: GTAACCTATTCAGGGTCCTAGC
GAPDH	XM_017321385.1	Forward: GGTTGTCTCCTGCGACTTCA Reverse: TGGTCCAGGGTTTCTTACTCC

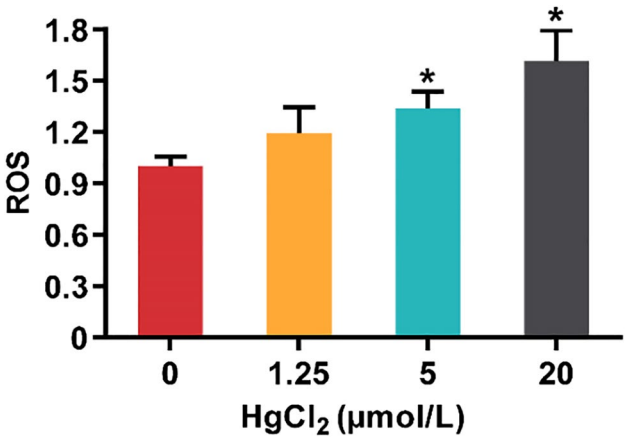

Fig. 2 Effect of exposure to $HgCl_2$ on oxidative stress. After exposure to $HgCl_2$, a dose-dependent increase in ROS was observed. Data were presented as the means ± SEM, n = 6. * Meaning a significant difference ($P < 0.05$) vs control group (dosage of 0 group)

$HgCl_2$ Decreased the Expression of Sirt1 and Increased the Expression of PGC-1α, and Affected the Ratio of Mfn2 to Drp1

Compared with the control group, $HgCl_2$-treated HEK-293 T cell contained significantly lower levels of the Sirt1, and higher expression levels of PGC-1α, except for the low-dose $HgCl_2$ group ($P < 0.05$). When $HgCl_2$ was given as a clear inhibition of Sirt1, the production of Drp1 increased and the levels of Mfn2 were decreased (Fig. 4A and B), which is consistent with the results of the qRT-PCR.

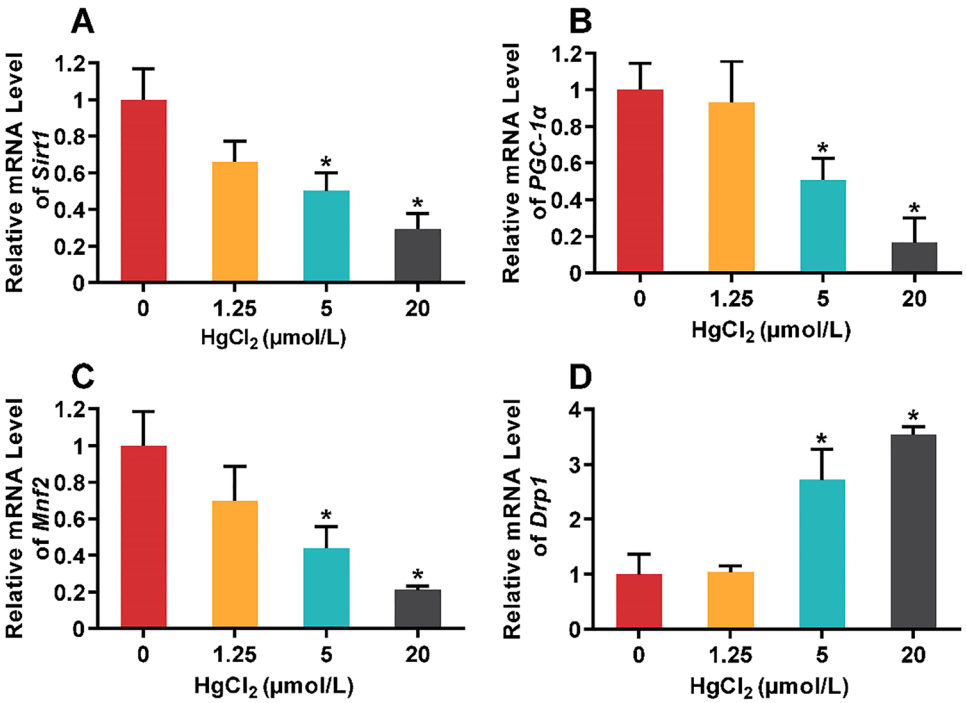

Fig. 3 Effect of $HgCl_2$ on Sirt1/PGC-1α signaling pathway in HEK-293 T cells. The relative mRNA levels of *Drp1* (**D**), *Mfn2* (**C**), *Sirt1* (**A**), and *PGC-1α* (**B**). Data were presented as the means ± SEM, n = 6. * Meaning a significant difference ($P < 0.05$) vs control group (dosage of 0 group)

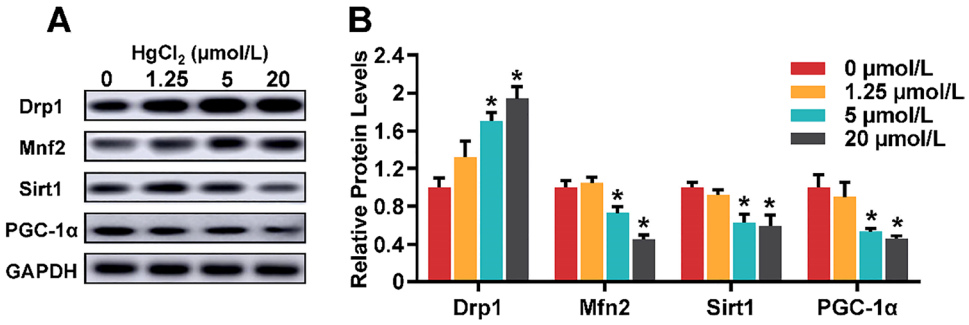

Fig. 4 Changes in Drp1, Mfn2, Sirt1, and PGC-1α levels in $HgCl_2$-treated HEK-293 T cells. Data were presented as the means ± SEM, n = 4. * Meaning a significant difference ($P < 0.05$) vs control group (dosage of 0 group)

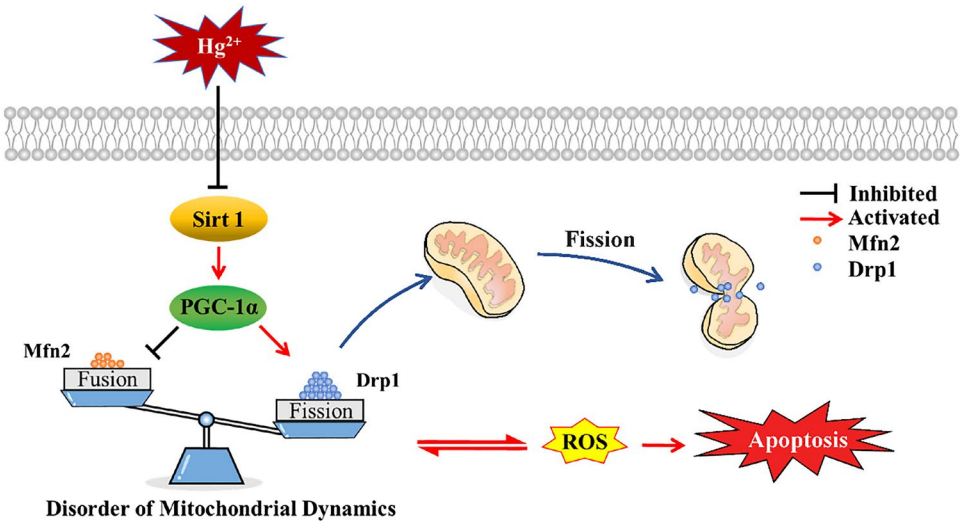

Fig. 5 Schematic diagram of $HgCl_2$-induced apoptosis in HEK-293 T cells. Mitochondrial dynamics disorder induced by $HgCl_2$ exposure activates oxidative stress in HEK-293 T cells via inhibition of the Sirt1/PGC-1α signaling pathway

Discussion

With the development of industries, mercury pollution in the global environment has become increasingly serious, which poses severe harm to human and animal health by affecting drinking water and air quality [30]. Therefore, the prevention and control of mercury poisoning have become a pressing issue facing all countries in the world [31]. Many studies have shown that inorganic mercury deposits itself in multiple tissues, such as pulmonary, liver, and kidney [32, 33]. The kidney is the most susceptible to the toxicity of ingested inorganic mercury, but side-effect-free pharmaceuticals are hitherto not available. In our study, the cell viability of HEK-293 T cells was significantly reduced by 5 and 20 μmol/L $HgCl_2$ treatment for 24 h with CCK-8 assays. Therefore, the result suggests that $HgCl_2$ exerts a cytotoxic effect on HEK-293 T cells.

$HgCl_2$ can cause oxidative stress in the liver, kidney, and brain of rats by producing excessive ROS production [32, 34]. Besides, $HgCl_2$ has been shown to induce oxidative stress in human erythrocytes [35]. Studies have shown that after 24 h of exposure to $HgCl_2$, SH-SY5Y cells significantly increased ROS production, and the viability decreased in a dose-dependent manner [36]. The level of ROS in HEK-293 T cells increased in a dose-dependent manner in our investigation, which is consistent with the test results of cell viability. Hence, our results revealed that oxidative stress caused by $HgCl_2$ causes damage to HEK-293 T cells.

Mitochondria are the main production source of ROS, and they also can produce ATP, which is the "power source" of cells. The morphological changes of mitochondria are regulated by mitochondrial fusion and fission, and the disorder of its dynamics can cause cell damage [37]. Mfn2 is involved in mitochondrial fusion, while Drp1 is the primary regulator of mitochondrial division. Under pressure, Drp1 forms a helical oligomer, which wraps the outer mitochondrial membrane and divides mitochondria [38]. Over mitochondrial fragmentation results in many ROS accumulation, which in turn ROS overload makes mitochondrial damage more serious [39–42]. Our results demonstrate that $HgCl_2$ exposure causes mitochondrial dynamics disorder and make mitochondria tend to fission. Thus, abnormal mitochondrial dynamics and oxidative stress caused by $HgCl_2$ may promote HEK-293 T cell damage.

PGC-1α mediates mitochondrial biogenesis and also regulates mitochondrial fusion and fission [43]. As an essential upstream regulator of PGC-1α, Sirt1 activates PGC-1α by regulating deacetylation to induce mitochondrial dysfunction and influence energy metabolism [44]. In the present study, our findings showed that $HgCl_2$ exposure decreases the levels of Sirt1 and increases PGC-1α in HEK-293 T cells. Previous research has shown that PGC-1α stimulates Mfn2 expression and downregulates Drp1 expression [45]. In this study, $HgCl_2$ exposure can downregulate the expression of Mfn2 and upregulate the expression of Drp1 in HEK-293 T cells, leading to excessive mitochondrial division. Thereby, our results suggest that $HgCl_2$ may cause HEK-293 T cell mitochondrial dynamics disorder by inhibiting the Sirt1/PGC-1α signaling pathway.

Mitochondria are a power house that play critical roles in cell differentiation, signaling transmission, and cell apoptosis. Mitochondrial fragmentation is a hallmark of apoptosis, at which time mitochondria tend to fission [46]. Hence, in this study, we confer that $HgCl_2$ exposure triggers mitochondrial dynamics disorder via promoting oxidative stress, leading to apoptosis in HEK-293 T cells (Fig. 5).

Conclusion

In conclusion, our study firstly demonstrates $HgCl_2$ causing mitochondrial dysfunction through the inhibition of the Sirt1/PGC-1α signaling pathway, eventually leading to apoptosis HEK-293 T cells. Our findings provide the possibility that activating the Sirt1/PGC-1α signal pathway is beneficial for treating kidney apoptosis induced by inorganic mercury exposure.

Author Contribution BQ Han: Conceptualization, Methodology, Data Curation, Writing–original draft. ZJ Lv: Conceptualization, Methodology, Investigation, Formal analysis. XM Han: Conceptualization, Methodology. SY Li: Conceptualization, Methodology. B Han: Conceptualization, Methodology. QY Yang: Methodology, Validation, Formal analysis. XQ Wang: Software, Formal analysis, Methodology, Data curation. PF Wu: Conceptualization, Investigation. JY Li: Methodology. N Deng: Software, Formal analysis. ZG Zhang: Conceptualization, Methodology, Project administration Writing–Review and Editing, Funding acquisition.

Funding This study was supported by the National Natural Science Foundation of China (31972754).

Data Availability The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval and Consent to Participate Not applicable.

Conflict of Interest The authors declare that they have no conflict of interest.

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