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Oxidative Stress and Kidney Glycation in Rats Exposed Cadmium

Eko Suhartono, Triawanti, Amin Setyo Leksono, and M. Sasmito Djati

***Abstract*—Cadmium (Cd) is a heavy metal and it was proposed in the formation of Reactive Oxygen Species (ROS) and Advance Glycation End Products (AGEs). The role of Cd induced oxidative stress and glycation in kidney has not been much studied. Thus our study aimed to measure the oxidative stress and glycation in kidney exposed to Cd. The present study was a true experimental study design to examine the impact of Cd exposure in renal rats *(Rattus novergicus)* male. The study involved 4 group, K0 was the control group, while the other (K1,K2,K3) was the case group with exposure of Cd in different concentration. For analyzing of the data, SPSS software version 17 was used and was examined by ANOVA test. The resulted showed that there are a significance differences of MDA, H_2O_2, SOD activity and AOPP between case and control group, but there are not MG and CC are not sgnificance differences. Our study showed Cd induced oxidative stress but not caused glycation reaction.**

***Index Terms*—AOPP, cadmium, glycation and oxidative stress.**

I. Introduction

Cadmium (Cd) is heavy metals which used in many industry, including semiconductor, manufacturing, welding, soldering, ceramics and painting [1]. Roughly 13,000 tons of cadmium is produced worldwide each year for nickel-cadmium batteries, pigments, chemical stabilizers, metal coatings and alloys [2]. The Agency for Toxic Substances and Disease Registry (ATSDR) has listed Cd among the top seven of the 275 most hazardous substances in the environment [3], [4]. Cd remains a source of concern for industrial workers and for populations living in polluted areas, especially in developed countries [5].

Cd is hazardous both by inhalation and ingestion and can cause acute and chronic toxicity [6]. The routes of Cd intake involve the lungs, intestines and skin [7]. Cadmium in the body is predominantly bound to metallothioneins. The cadmium–metallothionein complex is distributed to various tissues and organs and is ultimately reabsorbed in kidney tubuli [7]. There is no mechanism for the excretion of cadmium in humans. Thus Cd can accumulates throughout a lifetime inside the body. The half-life of cadmium in kidney cortex is 20–35 years [7].

Acute exposure to Cd causes dysuria, polyuria, chest pain, fatigue and headache [8]. Chronic poisoning typically was found to have occurred after several years of exposure and was characterized clinically by variable features of nasorespiratory involvement, such as emphysema, rhinitis, alteration of nasal mucosa, and anosmia, and by renal tubular dysfunction. Yellow tooth discolouration, mild anaemia, and disturbances in calcium metabolism, osteomalacia, and renal toxicity also were observed occasionally [9]. In humans, the largest amount of Cd is deposited in the kidneys, liver, pancreas and lungs [7], [10].

Clinical kidney damage has been demonstrated mainly in connection with occupational exposure. However, in the past couple of decades, exposure to level of cadmium found in the general population has been shown to result in subtle effects on the kidney, for example on renal tubular markers and bone [11]. Kidney cadmium have been measured both at autopsy and *in vivo* [9].

The mechanism Cd damage the kidney might through the formation of Reactive Oxygen Species (ROS) [12] and Advance Glycation End Products (AGEs) by nonenzymatic reaction [13].

The nonenzymatic reaction between reducing sugars and proteins, known as glycation, has received increased attention in nutritional and medical research. Nonenzymatic glycation is a complex series of reactions between reducing sugars and amino compounds [14].

The previous study described that the reaction of MG with ceruloplasmin may lead to decreased feroxidase activity in vitro [15]. In addition, the ferritin/MG/lysine system may lead to oxidative DNA damage via the generation of ROS by the Fenton-like reaction of free iron ions released from oxidatively damaged ferritin [16]. Based on previous research, methylglyoxal formation can be accelerated by metals in vitro. The proposed mechanism explained that the metal Mn+ (e.g., Fe^{2+}, Cu^{2+}, and so on) can catalyze the 2,3-enediol and formed MG and hydroperoxide [17]. The role of Cd in the formation of MG and Carbonyl Compound (CC) has not been much studied.

Various studies have been made on the cadmium-induced oxidative stress on kidney. Kevin Dzobo *et al* 2013, showed that Cd induced oxidative stress and depletes antioxidant enzymes in rat kidneys and testes [18]. In other studies of 95 patients Chronic Kidney Disease (CKD) in India showed that the serum MDA level was significantly raised and serum SOD level registered a significant decline in both non dialysis and hemodialysis groups compared with control. The SOD

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activity is decreased in CKD patients owing to increased ROS load such as hydrogen peroxide, which is a known suppressant of SOD activity [19].

ROS compounds were involved in production of advance oxidation protein products (AOPP) AOPP is dityrosine containing cross linked protein products, a definition that is important as it excludes protein aggregates that are formed by disulphide bonds as a result of oxidative stress. Therefore, AOPP is a good oxidative stress marker, which originates under oxidative and carbonyl stress and increase global inflammatory activity [20]-[24].

AOPPs are not innocent end products of activation of macrophages: they are biologically active molecules capable of mediating oxidative stress and respiratory burst in monocytes [25].

At the respiratory burst, there was a rapid uptake of molecular oxygen and transformation into reactive oxygen compounds, which is a representation the host defense mechanisms in the inflammatory site. It is important that relevant reactive oxygen compounds physiological concentrations able to modulate the redox-sensitive signaling cascade and improve immunological cellular function [26]. Our study aims to measure oxdative stress and glycation in kidney exposed to Cd.

II. Material and Methods

The present study was a true experimental study design to examine the impact of Cd exposure in renal rats *(Rattus novergicus)* male, Sprague-Dawley furrow, healthy and have normal activity with 8-10 weeks of age and weighing 300±10 grams.

All rats were caged separately for adaptation for one week. During the acclimation period and the mice were fed the same drinking water treatment period, ie C-05 pellets and PDAM water as drinking water. Before being treated, rats were fasted for 1-2 hours would be to ensure that the rat stomach empty.

The study involved 4 groups of 3 female rats *(Rattus novergicus),* where one group (*K*0) was the control group, while the other was the case group with exposure of Cd. The control group rats were given 2 ml of distilled water with a sonde every morning while in the treatment group rats were exposed Cd in the different concentration. *K*1 = administration of Cd 0.003 mg/L, *K*2 = Cd administration of 0.3 mg/L, and *K*3 = Cd administration of 3 mg/L. All groups of rats were provided ad libitum for 4 weeks.

After rats is surgery, serum and kidneys were taken and immediately fixed in phosphate buffer solution pH 7. Then the kidney was cut into small pieces and ground to form a liquid. Subsequently, 5 ml of the solution was taken and centrifuged at 3500 rpm for 10 minutes. The top layer of 200 mL were taken to be examined.

A. Hydrogen Peroxide Assay

Determination of H_2O_2 concentration by the modified FOX2 method [27]. Solutions measured spectrophotometrically at λ = 560 nm. Standard and test solutions consisted of 1 M H_2O_2 200 µL and 200 µL serum, respectively, with the addition of 160 µL PBS pH 7.4, 160 µL $FeCl_3$ (251.5 mg $FeCl_3$ dissolved in 250 ml distilled water) and 160 µL o-fenantroline (120 mg o-phenantroline dissolved in 100 ml distilled water) for both solutions. The composition of the blank solution was identical to that of the test solution, except for absence of $FeCl_3$ in the blank. Subsequent to preparation, all solutions were incubated for 30 minutes at room temperature, then centrifuged at 12,000 rpm for 10 minutes, and the absorbance of the standard (As), test (Au) and blank (Ab) solutions measured at λ=505 nm, using the supernatant of each solution.

B. Malondyaldehide Assay

MDA was measured by the method of Buege and Aust [28]. The colour was measured spectrophotometrically at 532 nm. Serum in the homogenization of 100 mg. Then add 1 mL aquadest then disposed of in thee pendorf. After that added 100% TCA 100 uL, 1% Na-Thio 100 uL and 250 uL 0.1 N HCl. The solution is heated at a temperature of 1000 ₀C for 20 minutes. Then centrifuged to 3500 rpm for 10 minutes. Supernatant was taken. After that, add distilled water up to 3500 uL. The result is read by a spectrophotometer with a maximum wavelength of 500-600 nm.

C. Superoxide dismutase Assay

The SOD activity in supernatant was measured by the method of Misra and Fridovich [29]. The supernatant (500 μl) was added to 0.800 ml of carbonate buffer (100 mM, pH 10.2) and 100 μl of epinephrine 3 mM). The change in absorbance of each sample was then recorded at 480 nm in spectrophotometer for 2 min at an interval of 15 sec.

D. Methylglyoxals Assay

Methylglyoxals are estimated according to the modified method of Racker [22]. Twenty-five µl of samples was added to 350 µl of DNPH [0.1% DNPH in 2N HCl]. Then to each tube 2.125 ml of distilled water was added. Then it was incubated for 15 minutes at 37^0C. After the incubation 1.5 ml 10% NaOH was added and absorbance was read at 576 nm using spectrophotometer. MG levels are expressed in percent absorbance MG and dicarbonyl absorbance [30].

E. AOPP Assay

Kidney homogenat AOPP measurement were made by spectrophotometric methods as describe by Witko-Sarsat *et al* [31].

F. Carbonyl Compound Assay

Sample derivatization. Two 1-µL aliquots are needed for each sample to be assayed. Samples are extracted in a final concentration of 10% (w/v) TCA. The precipitates are treated with 500 µL of 0.2% DNPH or 500 µL of 2 M HCl. Samples are incubated at room temperature for 1 h with vortexing at 5-min intervals. The proteins are then precipitated by adding 55 µL of 100% TCA. The pellets are centrifuged and washed three times with 500 µL of the ethanol:ethyl acetate mixture. The pellet is then dissolved in 600 µL of 6M guanidine hydrochloride. The carbonyl content is determined by reading the absorbance at the optimum wavelength 390 nm [28].

G. Statistical Analysis

Data are presented as means ± SD. The differences were examined by the ANOVA test. For all outcomes, a nominal

p-value of $p < 0.05$ was considered significant.

III. Result and Discussion

TABLE I: SOD Activity, H_2O_2 and MDA Levels in Serum Rats Exposed to Cadmium

Parameters	*K*0	*K*1	*K*2	*K*3	*P*
MDA (μM)	529± 34,95	567,38± 48,32	567,38 ±48,32	704,63 ±56,85	0,000
H_2O_2 (μM)	4,35± 0,80	12,72± 4,11	12,72± 4,11	18,35± 2,70	0,000
SOD (IU/mL enzim)	12,81± 2,33	12,73± 2,51	12,73± 2,51	8,08± 2,62	0,004

The average levels of MDA, H_2O_2 and SOD activity are presented in Table I. ANOVA test results showed (Table I) that there were significant differences between case and control groups ($p<0.05$). The increased of H_2O_2 levels and decreased of SOD activity indicates that oxidative stress has occurred in rats exposed to Cd.

Occupational exposure to Cd has been associated with occurence of increased oxidative stress. Oxidative stress is a harmful condition that occurs when there is an inbalance between ROS, including superoxide, hydrogen peroxide and hydroxyl radicals, and/or by inadequate antioxidative defences, including SOD, catalase, and peroxidase. An interesting mechanism explaining the indirect role of Cd in free radical generation was presented some years ago [10].

SOD is considered a key enzyme in the regulation of intracellular concentrations of ROS. SOD acts as the first line of defense against ROS, dismutating superoxide to H_2O_2. SOD acts as the first line of defense against ROS, dismutating superoxide to H_2O_2. Thus, increased SOD activity showed that it plays a positive role in controlling the cellular level of these ROS and/or repairing oxidative damage against free radicals by Cd stress [32].

H_2O_2 is an even less reactive species that is uncharged and can diffuse across membranes through aquaporins. Despite its low reactivity, some proteins contain specific cysteine residues that are prone to oxidation by hydrogen peroxide, which are critical to hydrogen peroxide-based signaling systems. H_2O_2 can be converted to the radical hydroxyl, a highly reactive species. H_2O_2 and other toxic oxygen species production in cellular compartments and result in acceleration of lipid peroxidation and other oxidative damage [33], [34].

The increased of MDA levels in serum rats exposed to Cd indicate the increased of lipid peroxidation. It is known that metal-induced generation of oxygen radicals results in the attack of not only DNA but also other cellular components involving polyunsaturated fatty acid residues of phospholipids, which are extremely sensitive to oxidation [12].

The overall process of lipid peroxidation consists of three stages: initiation, propagation and termination. Initiation, the first stage, involves the attack of a ROS capable of abstracting a hydrogen atom from a methylene group in the lipid. The presence of a double bond adjacent the methylene group weakens the bond between carbon and hydrogen so the hydrogen can be more easily removed from the fatty acid molecule. Fatty acids with no double bonds or with onedouble bond can undergo oxidation but not a chain lipidperoxidation process [7].

The process of hydrogen abstraction leaves behind a fatty acid having one unpaired electron. When oxygen is present in the surrounding tissues, the fatty acid radical can react with it leading to the formation of lipo-peroxyl radicals (ROO•). Once formed, lipo-peroxyl radicals (ROO•) can be rearranged *via* a cyclization reaction to endoperoxides (precursors of malondialdehyde) with the final product of peroxidation process being MDA. MDA is mutagenic in bacterial and mammalian cells and carcinogenic in rats. Increase in lipid peroxidation with increased MDA levels has been observed in a cadmium-induced experimental group of wistar albino rats. It has been reported in other research that administration of Cd via different routes causes increased lipid peroxidation in membranes of erythrocytes and tissues such as the liver, kidney, brain and testes where MDA is used as an indicator of oxidative damage [4], [7], [12].

MDA is one of the main manifestations of oxidative damage and has been found to play an important role in the toxicity of Cd. MDA is well-known lipid peroxidation indicator and has been found to increase in the liver and kidneys after Cd exposure. Eko Suhartono *et al*. 2013 in his research showed that the administration of Cd caused significantly increase of MDA and peroxide levels as compared to the control group ($p<0.05$) [4], [30]. The results of other studies showed that ethanol and Cd increased the serum and liver MDA concentrations 24 h after administration [4]. Haki Kara *et al* 2002 suggest that single doses of different concentrations of Cd are administered the dose dependent increase in MDA levels in agreement with this knowledge [35].

TABLE II: AOPP, CC and MG Levels in Renal Rats Exposed to Cadmium

Parameters	*K*0	*K*1	*K*2	*K*3	*P*
AOPP (μM)	4,51± 0,23	6,55± 0,45	6,83± 0,61	9,40± 1,40	0,000
Carbonyl Compound (nM)	2,55± 0,99	2,93± 0,42	2,81± 0,52	3,20± 0,40	0,208
Methylglyoxal (%)	20,88± 5,41	25,39± 5,21	29,49± 9,73	29,73± 8,62	0,232

The levels of AOPP, CC and MG was evaluated. ANOVA test resulted showed that there were not significant diffrences in the levels of CC and MG.

Heavy metal was proposed in the formation of advance glycation end products (AGEs) by nonenzymatic reaction. Glycation is nonenzymatic reaction between reducing sugars and proteins. Voziyan et al proposed that heavy metal can accelerate the formation of compounds dicarbonyl [e.g., glyoxal (GO), methylglyoxal (MG) and 3 deoxyglucosone] [13], [14].

MG as a side-product of glycolysis arises from an increased flux during hyperglycemia. MG has been postulated to play a role in the development of hypertension [36]. Studies using animal model and cell cultures showed a significant increase in blood pressure to coincide with elevated MG level in plasma and aortic tissues [37], [38]. However, functional links between MG biogenesis and hypertension, in part

mediated by ROS and AGEs, have only been documented in rat model but not yet in humans under these conditions.

In Table II shows that increasing concentrations of Cd has no Increased levels of Cd does not make a significant difference in kidney rats. That indicates that exposure to Cd is not caused glycation reactions in the kidneys. On the other hand exposure to Cd caused an increasing of AOPP level that indicates Cd caused inflammation in kidney rats.

According to previous studies AOPP may represent a novel class of proinflammatory mediators acting as a mediator of oxidative stress and monocyte respiratory burst. The monocyte is thus, at the same time, the elective cellular target of AOPP and a potential source of oxidants inducing AOPP [31].

A close correlation was observed between AOPP and neopterin, the monocyte activation marker. This selective relationship between AOPP and monocyte activation was further established with positive correlations between AOPP and TNF-α and its soluble receptors, and, to a lesser degree, with IL-1Ra, although these correlations tended to be of only borderline significance when values were corrected for creatinine clearance [22].

Exposure of Cd activated cells to form a reactive oxygen compounds. This event called respiratory burst involving the NADPH oxidase activation. At the respiratory burst, there was a rapid uptake of molecular oxygen and transformation into reactive oxygen compounds, which is a representation of the host defense mechanisms in the inflammatory site. It is important that relevant reactive oxygen compounds physiological concentrations able to modulate the redox-sensitive signaling cascade and improve immunological cellular function [24].

Reactive oxygen species such as hydrogen peroxide, superoxide anion, hydroxyl radical, etc can trigger oxidative damage to macromolecules, leading to lipid peroxidation, amino acid chains oxidation, cross links protein formation, polypeptide chain oxidation forming protein fragmentation, DNA strands ruptured. Radical oxygen compounds were involved in production of AOPP [25].

In the past, studies on the interactions between proteins and oxidants have focused on the structural changes induced by oxidants generated by water pulse radiolysis, including superoxide and hydroxyl radicals. Such studies have demonstrated that structural modifications of proteins (selective loss of an amino acid, fragmentation, or aggregation) were highly dependent on the nature of the oxidant. The formation of AOPP could be induced in control plasma by chlorinated oxidants such as chloramines or hypochlorus acid. Of note, the *in vitro* formation of AOPP was much lower when proteins were submitted to H_2O_2 compared to identical concentrations of chlorinated oxidants. Moreover, the formation of AOPP using purified human serum albumin waqs clearly correlated to the concentration of chlorinated oxidant added [31].

Since AOPP formation is optimal with chlorinated oxidants, it is interesting to speculate that its formation in vivo might result from enzymatic activity of phagocyte-derived Myelopeoxidase (MPO) [22].

AOPPs are produced during oxidative stress and inflammation as a result of MPO activity in activated neutrophils acting on hypochloric acid and chloramines; these are a reliable marker to measure the oxidative modification of proteins [39]. MPO is an haeme-containing enzyme which secreted by the phagocytes after an activation from respiratory burst system. MPO are usually used as tissues neutrophil accumulation and neutrophil activity marker on plasma assays. Myeloperoxidase use hydrogen peroxides to oxidize amount of aromatic species (RH) by one electron mechanism to form aromatic radical (R●). This is typical, therefore they are ready to oxidize the strong non radical reactive oxygen species, the HOCl ions. HOCl is reactive oxygen species that produced by neutrophils and very bactericidals [17].

IV. Conclusion

The results of this study concluded that exposure to cadmium causes oxidative stress in the kidneys, but not caused glycation reaction.

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