8-Hydroxy-2-Deoxyguanosine as Oxidative DNA Damage Biomarker of Medical Ionizing Radiation: A Scoping Review

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ABSTRACT

Background: Recent studies reported the significant expansion using 8-Hydroxy-2-Deoxyguanosine (8-OHdG) as a biomarker of oxidative Deoxyribonucleic Acid (DNA) damage among human populations exposed to medical ionizing radiation, but a generalized overview about this topic has not been conducted yet.

Objective: This scoping review of published literature examined recent trends in utilizing 8-OHdG biomarker to measure oxidative DNA damage induced by medical ionizing radiation and possible factors that may influence the 8-OHdG level.

Material and Methods: Literature search was conducted in PubMed, Scopus and ProQuest databases for publications from 1984 to 2/12/2020. Included articles were: cohort studies, case-control studies, and cross–sectional studies, randomized and nonrandomized controlled trials. Excluded articles were: editorials, letters, personal opinions, newspaper articles, study plans, protocols, qualitative studies, case reports and series, in-vivo and vitro studies, animal research studies, reviews and meta-analyses.

Results: According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we screened 141 articles, and 10 eligible studies met our inclusion criteria. All studies measured 8-OHdG as an oxidative DNA damage biomarker. The study results were contradictory concerning the relationship between the radiation dose and 8-OhdG level. 8-OHdG was mostly measured by enzyme-linked immunosorbent assay (ELISA) using urine samples. Sample size varied between (n=25-230) and included patients who underwent medical radiation procedures or workers exposed to ionizing radiation during their jobs.

Conclusion: This scoping review findings showed 8-OHdG can be used as a promising biomarker to detect oxidative damage, resulting from medical ionizing radiation exposure despite external factors that may influence 8-OHdG levels.

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Keywords

Medical Ionizing Radiation; 8-Ohdg; Biomarker; Enzyme-Linked Immunosorbent Assay; Oxidative DNA Damage; Reactive Oxygen Species; Scoping Review

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Introduction

After the discovery of X-ray by Rontgen at the end of the nineteenth century, the danger of ionizing radiation was recognized [1]. The main man-made source of radiation exposure is medical radiation. Every year, about 5 billion imaging exams are conducted worldwide [2]. The advent of diagnostic imaging and interventional

radiology has raised concerns about the possible risk of ionizing radiation exposure to healthcare workers using these technologies [3]. It has long been believed that cancer risk is increased by ionizing radiation. In fact, the International Agency for Cancer Research of the World Health Organization has recently officially identified X-rays and gamma rays as "carcinogens" [2]. Epidemiological evidence supports an elevated risk of cancer incidence at the amount of radiation typically received by cardiac imaging patients [4].

Today, possible pathological changes arising in radiation workers need to be closely examined. Ionizing radiation may induce elevated levels of reactive oxygen species, oxidative Deoxyribonucleic Acid (DNA) damage, and immunosuppression [3]. Due to its mutagenic ability, 8-hydroxy-2' -deoxyguanosine (8-OHdG) is by far the most studied oxidative DNA lesion. Therefore, assessment of human oxidative stress with 8-OHdG is frequently measured by urinary excretion [5]. It has been established as a sensitive biomarker for the evaluation of oxidative DNA modification [6,7]. We conducted a scoping review on the 8-OHdG measurement as a biomarker of oxidative DNA damage due to ionizing radiation, focusing mainly on ionizing radiation of medical procedures. A scoping review can provide the comprehensive information needed to understand the effect of radiation on 8-OHdG level and identify any gaps in recent studies [8].

Synopsis

Development of Research Questions

A scoping review was conducted with the aim to explore, chart, and summarize the published studies on the use of 8-OHdG biomarker to assess oxidative DNA damage on subjects exposed to medical ionizing radiation. Furthermore, we identified research methods and models used in oxidative stress research due to medical ionizing radiation (e.g., purposes, contexts, study populations, sample sizes, designs, and methods for data collection). Oxidative stress effects recorded in studies on oxidative stress due to medical ionizing radiation are also discussed. We addressed the following research questions identified by the research team to achieve the purpose of this study. The questions are:

1. Is 8-OHdG a promising biomarker of oxidative DNA damage of exposure to medical ionizing radiation?
2. What are the possible factors that may influence 8-OHdG levels?

For these reasons, a scoping review was conducted to systematically map the research in this field and to identify any possible knowledge gaps.

Material and Methods

Protocol and registrations

In this review, we used the prespecified Population, Intervention, Comparison and Outcome criteria for eligibility and part of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model to report the literature. This is a scoping review with the aim of revealing existed literature about the use 8-OHdG biomarker to detect DNA oxidative damage caused by medical ionizing radiation, not a meta-analysis or effectiveness review.

Inclusion criteria

The following study designs were included: Cohort studies, case-control studies, cross–sectional studies, randomized and nonrandomized controlled trials.

Studies included focused on all ages, who were receiving ionizing radiation from medical procedures from 1984 to 2/12/2020.

Only abstracts and/or articles published in English language were accepted.

Exclusion criteria

The following study designs were excluded:

editorials, letters, personal opinions, newspaper articles, study plans, protocols, qualitative studies, case reports and series, in-vivo and vitro studies, animal research studies, reviews and meta-analyses.

Information sources/ search strategy

We searched through the following databases: PubMed, Scopus and ProQuest. In coordination with a librarian, a specialist in health-related literature search, the search strategy and database selection were created. In PubMed, the search plan was implemented and adapted to all other databases. The search took place in December 2020. PubMed (1992–December 2, 2020), Scopus (1987–December 2, 2020) and ProQuest (1992–December 2, 2020) were among the databases searched. Within the search strategy, we used the following terms (8-Hydroxy-2 -Deoxyguanosine OR 8-OHdG) AND (ionizing OR radiation OR radiography OR catheterization OR radiotherapy) NOT (ultraviolet radiation OR UV OR ultraviolet) NOT (animal OR rats OR mice). Text has been linguistically validated in cooperation with a publishing and linguistics expert in the Research and Publication Office, Faculty of Medicine, Public Health and Nursing UGM.

Search/ study selection

Using Microsoft Excel (version 15), the documents were archived and analyzed. While screening the literature, there were three choices: "included", "excluded" and "maybe". All the literature selected were double-checked by co-authors. Moreover, to look for similar additional research, we checked the reference lists of reported papers.

Summary measures

To collect data from articles selected, we used a structured outline for the scoping assessments (as shown in Table 1) and derived the idea from Peter's guide of conducting systematic scoping reviews [9]. We summed up the data of the included studies with the following information: Study aims, study population/sample size, specimen, results, and limitations (see Table 1).

Results

Studies selection process

In the literature scan, we found 141 studies. After duplication was eliminated, we had 104 studies to assess. Of these, 53 were selected after the titles were screened for abstract screening. There were 17 full text articles left to study after reading the 53 abstracts. As shown in Figure 1, we used a PRISMA diagram, explaining the literature review process with a total of 10 manuscripts included in the final review from the searches in PubMed, Scopus and ProQuest. The data extraction for the 10 studies included is shown in the Table 1. Five of the included studies were observational [10-14], two studies were cross-sectional study [15,16], one study was case control [17], one study was prospective [6] and one study was retrospective [18]. There were variations in the design of the studies, power calculations and the number of subjects in the studies (n = 25–230), but 8-OHdG biomarker was measured in all studies. Also, the ionizing radiation was from medical sources in all studies. In general, the most common measurement method of 8-OHdG was the enzyme-linked immunosorbent assay (ELISA) kit [10,11,13,16-18] and the most common specimen used in studies was urine [12-14,15-18]. The uniqueness of this study is reviewing the use of 8-OHdG as a biomarker of oxidative DNA damage for patients and workers exposed to medical ionizing radiation.

8-OHdG measurement methods

The study populations in the literature included were as shown in Table 1, with pediatric patients who undergo cardiac catheterization [6], radiation workers [11,15,18], radiography

Table 1: The summary of the included studies.

Author and year	Aims	Study population/ Sample size	Specimen	Results	Limitations
Kato 2015 [6]	Determine the utility of urinary 8-OHdG in children undergoing cardiac catheterization as a sensitive biomarker for radiation-induced cellular DNA damage	38 subjects: 19 child as case group, 10 healthy children and 9 children under sedation as control group	Urine samples at baseline and 24-48 hours after cardiac catheterization procedure.	17.3 at baseline and increase to 44.4 (24-48 h) after procedure (p =.0001). In children undergoing diagnostic cardiac catheterization, 8-OHdG could be a sensitive biomarker.	1. The sample size was small, 2. All the subjects were from the same institution, 3. Did not collect dose-area product data, 4. The possibility that patients who received larger doses of contrast media developed asymptomatic acute renal failure.
Chen 2019 [10]	Measuring and determined the relationship among occupational radiation level, oxidative damage and DNA methylation status in interventional physicians	117 interventional physicians and 117 controls	Venous blood was collected from the subjects in the morning	3.014±1.34 of interventional physicians and 2.635±1.28 for control (p-value 0.028). 8-OHDG was higher in interventional doctors than in controls.	1. Only long term indices of oxidative damage markers were considered, 2. Short-term oxidative stress indicators such as superoxide dismutase, catalase, and glutathione (GSH) peroxidase were not included in the study, 3. lack of information on sample sources, heredity, living environment, diet, and other factors were not included
Gao 2019 [11]	Investigate the effect of ionizing radiation on 8-OHdG in human peripheral blood	230 radiation workers and 8 radiotherapy patients	Venous blood samples were drawn from radiation workers. While for patient venous blood samples were drawn before and after each radiotherapy course once a week, 5 times in total	1. Diagnostic radiology 80.93 (23.71), 2. Radiotherapy 91.44 (32.98), 3. Nuclear medicine 95.63 (34.83), 4. Interventional radiology 120.29 (63.88) (p <.001). Radiotherapy patients: 196.71 (42.66). 8-OHdG may be a useful biomarker reflecting oxidative damage among workers occupationally exposed to low-dose radiation. no linear correlation between serum 8-OHdG levels and accumulative radiation dose for radiotherapy patients.	The authors did not disclose any limitations

Author and year	Aims	Study population/ Sample size	Specimen	Results	Limitations
Turnu 2018 [12]	Evaluate the oxidative and DNA damage in 59 catheter ablation patients	49	4 urine samples: pre- catheter ablation, 3 h post, 24 h post and 48 h post	Pre-catheter ablation: 4.6, 3 h post: 4.8, 24 h post: 4.85, 48 h post: 5.5. 8-OHdG increased significantly after 24 h than baseline ($p < 0.05$ vs. baseline). 8-OHdG is a reliable indicator of DNA damage by linking its variation with the increase in percentage of DNA breaks.	The author did not disclose any limitations
Yamaza-ki 2005 [13]	Estimate the oxidative stress caused by radio-therapy	72	4 urine samples: pre-treatment, 1 week post, post complete treatment and 1-2 months post	Breast cancer: 4.9±3.3 Esophageal cancer: 7.7±7.2 Prostate cancer: 12.6±9.1 Tongue cancer: 17.6±9.5 cervical cancer: 10.0±1.4. Radiotherapy did not cause changes in the excretion level of urinary 8-0HdG in patients with breast, esophageal and tongue cancer. However, radiotherapy reduced 8-0HdG excretion levels in patients with cervical cancer, whereas interstitial radiotherapy transiently increased t hese levels in patients with prostate cancer.	The authors did not disclose any limitations
Pinch 2000 [14]	Investigate the course of biomarkers and their relevance in patients with different types of chronic synovitis of the knee treated with radiation synovectomy with 165 D-ferric- hydroxide	25	baseline morning urine and 20 h post therapy	3.1±3.4; median, 2.27. there is no significant oxidative DNA damage due to radiation syno-vectomy using 165-dysprosium ferric hydroxide (DFH)	Biomarkers of cytogenetic dam-age show marked inter individual variations as a result of various exogenous and endogenous factors. The use of a protocol that assessed levels of biomarkers just before and 4 and 20 h after treatment reduced the probability that other factors might have influenced the results.

Author and year	Aims	Study population/ Sample size	Specimen	Results	Limitations
Salehi 2020 [15]	Examine the level of 8-OHdG in urine radiographers as the biomarker of oxidative damage due to ionizing radiation and compare this biomarker with collective effective doses.	70 subjects, 2 groups: 35 radiation worker and 35 non radiation worker	Urine samples at the end of shift work	Radiation worker: 259.4±31.07 Non-Radiation worker: 141.1±21.8 (p=0.009). The concentration of 8-OHdG in the urine of radiation workers had significant correlation with the collective effective dose.	The author did not disclose any limitations
Erhola 1997 [16]	Evaluate Urinary 8-OHdG creatinine levels of lung cancer patients by ELISA using a monoclonal antibody N45.1 during radiotherapy and chemotherapy	89	Urine samples were obtained from each individual at the first morning voiding	Overall: 22.6±13.0 and 19.4±8.5 for control. In in SCC: 27.2±17.4, non-SCC: 19.8±8.6. Significantly higher ($p < 0.05$) compared to the matched controls and to non-SCC patients. SCC, small-cell carcinoma (means ± SD).	The authors did not disclose any limitations
Himmetoglu 2014 [17]	Examine serum levels of 8-OHdG in children with scoliosis who had got whole spine radiograph two times during the last year	52 participants: 31 children with adolescent idiopathic scoliosis and 21 age-matched healthy children	5 mL of venous blood samples were collected within 3 h after the whole spine radiography	2.51 (0.30-12.00) ($p<0.001$). X-ray exposure causes increased 8-OHdG level	1. 8-OHdG level before and after the radiography had been assessed, and time dependent changes in the levels of measured parameters had been evaluated, more reliable data would have obtained, 2. To clarify the carcinogenic effect of repeated X-ray exposure in children with scoliosis, frequency 8-OHdG adducts in DNA of leukocyte should be examined at least six months after the radiography.
Mrdjanovic 2020 [18]	Determination of DNA damage among hospital personnel after accidental consumption of milk	160 participants: 80 radiation worker and 80 healthy control	Urine samples	6.59 irradiation worker and 4.48 control group. increased incidence of 8-OHdG level among hospital workers exposed to low-doses of Ionizing Radiation	Further investigations are required in order to more closely reveal the cumulative effect of exposure to mixed radiation/chemical agents with different action mechanisms

8-OHdG: 8-hydroxy-2' –deoxyguanosine, DNA: Deoxyribonucleic acid, ELISA:Enzyme-linked immunosorbent assa, SCC: small cell carcinoma

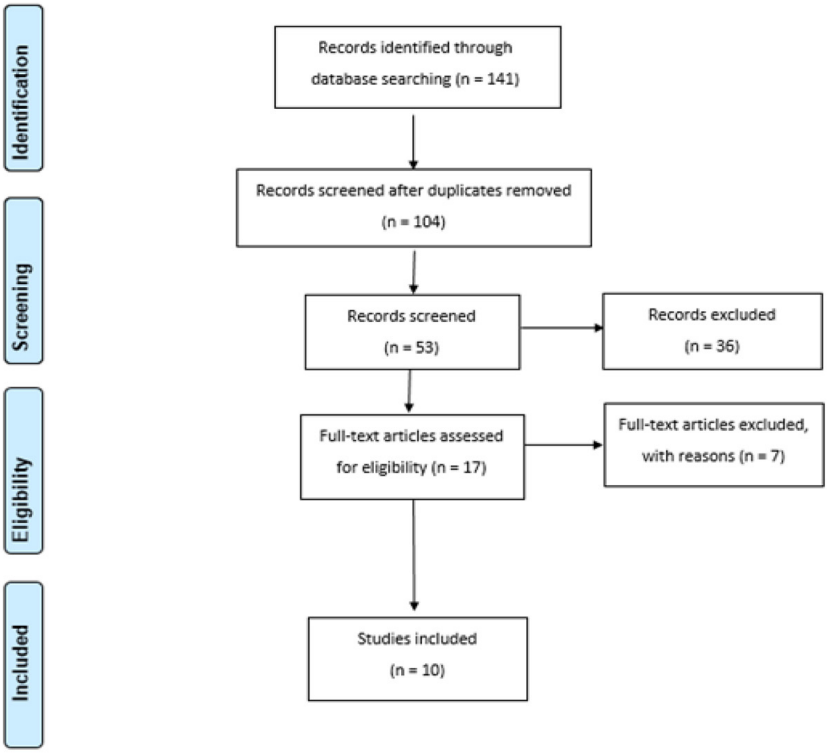

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the selection method for literature search.

scoliosis patients [17], interventional physicians [10], catheter ablation patients [12], radiotherapy patients [11,13,16] and arthritis patients who underwent radiation synovectomy [14].

The most common analytical method used for analysis of the 8-OHdG level in the included studies was ELISA [10,11,13,16-18]. Some different methods were used for analysis of 8-OHdG, including competitive immunochromatography with ICR-001 [6], Gas Chromatography Mass Spectrometry (GC-MS) analysis, Liquid Chromatography–Mass Spectrometry (LC-MS/MS) [12] and High-Performance Liquid Chromatography (HPLC) [14]. There were only two types of samples used in the selected studies: blood and urine. In this review, the percentage of studies that used urine samples [6,12-16,18] was higher than those that used blood samples [10,11,17].

There was a significant difference in the times of sample collection from the study participants and a difference in the number of samples regardless of whether they were blood or urine samples. This difference is attributed to the fact that the study participants are workers in the field of radiation who are exposed to radiation on a daily basis, or patients who were exposed to a regular radiation dose as they underwent a medical radiological procedure. In studies that were focused on collecting samples from radiation workers, the sample collection ranged between collecting urine samples at the end of shift work [15] and collecting venous blood samples in the morning [10]. The other studies did not state the time of collecting, but were limited to referring to the type of sample in terms of it being one blood sample [11] or one urine sample [18].

In the studies that focused on collecting samples from patients, the difference was large according to the type of procedure that the patient underwent. For example, for patients, who have undergone radiotherapy, there were

4 urine samples: pre-treatment, 1 week post, post complete treatment and 1-2 months post [13]. Blood samples were obtained once a week before and after each course of radiotherapy, with 5 times in all [11]. Urine samples were collected from each person at baseline voiding on the first morning and 2 months after, 5 times in all. [16]. For children who underwent cardiac catheterization, urine specimens were collected at baseline and 24-48h after the heart catheterization [6]. Meanwhile, children with scoliosis, who underwent whole spine radiography, the blood samples were collected within 3h after the procedure [17]. Four urine samples were collected from catheter ablation patients: pre-catheter ablation, 3h post, 24h post and 48h post [12], and from patients undergoing radiation synovectomy treatment with 165D-ferric-hydroxide, baseline morning urine and 20h post therapy [14].

Is 8-OHdG a biomarker of oxidative DNA damage of exposure to medical ionizing radiation?

The correlation between medical ionizing radiation and the level of 8-OHdG was evaluated by several distinct findings that may indicate the existence of the 8-OHdG relationship with medical ionizing radiation by proxy. The outcomes of the 10 studies described DNA damage through the level of 8-OHdG and the relation between medical ionizing radiation and 8-OHdG level through measurements of 8-OHdG level by urine [6,12-16,18] or blood [10,11,17].

In one study, the authors suggested many options of the relationship between radiotherapy and 8-OHdG level, and the difference of relations was based on the type of cancer that patients have when they undergo the radiotherapy course. There was an increasing in the 8-OHdG level of patients with prostate cancer after radiotherapy course. There was a decrease in 8-OHdG level after radiotherapy course for patients with cervical cancer, while 8-OHdG level did not change after radiotherapy course for patients who are suffering from breast, esophagus and tongue cancer [13]. In the Gao et al, study, serum 8-OHdG levels decreased after four radiotherapy treatment sessions, from 196.71 to 147.21 ng/mL. They claimed that there was no linear association between the cumulative exposure dose and 8-OHdGG in their discussion [11].

In another study, the authors suggested that there is no significant oxidative DNA damage due to radiation synovectomy using 165-dysprosium ferric hydroxide (DFH), i.e. the chance of malignancy will not increase [14]. Regarding the positive relationship between medical ionizing radiation and 8-OHdG level, the 8-OHdG levels for radiation workers exposed to medical ionizing radiation were higher compared to those who are not working in ionizing radiation procedures [10,11,15,18]. Moreover, several studies found the patients who were exposed to ionizing radiation had higher 8-OHdG levels compared with healthy people who were not exposed to medical ionizing radiation [6,12,16,17].

What are the possible factors that may influence 8-OHdG levels?

Several studies have shown some factors that may influence the levels of 8-OHdG caused by exposure to ionizing radiation in the included studies. One study suggested that 8-OHdG levels for patients who underwent radiotherapy course were significantly higher in patients with small cell carcinoma (SCC) compared to non-SCC patients and matched controls [16]. 8-OHdG has been correlated with multiple cancers, suggesting that patients typically have higher 8-OHdG levels than healthy people, which may be a confusing factor [11]. Stage and basic characteristics of cancer groups affected the range of excretion 8-OHdG [13]. Furthermore, when interpreting the concentrations of biomarkers of cytogenetic damage in terms of malignancy hazard in patients with chronic synovitis receiving radiation synovectomy, the underlying disease

should be considered [14].

Also, 8-OHdG levels were influenced by working duration and job classification. The interventional radiology workers have the highest 8-OHdG levels than other radiation workers even though they are all exposed to medical ionizing radiation [11]. Meanwhile, another study suggested that the nuclear medicine group also had the highest urine concentration of 8-OHdG among the other radiographers [15]. Unplanned intake of milk for radiation workers with excess aflatoxin concentrations could lead to greater value of identified DNA damage biomarkers [18].

Many confounding variables can influence the level of 8-OHdG, such as age, sex, and smoking habits. Smoking evaluations showed that smokers who were irradiated employees had higher values of 8-OHdG compared to non-smoking irradiated workers [18]. Conversely, another study suggested that there were no major variations in gender or smoking behaviors between the groups. In the study, diet was unlikely to be a confounding factor since most patients were hospitalized during the treatment and were thus given a regular hospital diet [16].

Discussion

Summary of evidence

The aim of this scoping review was to recognize available literature on the use of 8-OHdG as an oxidative DNA damage biomarker due to medical ionizing radiation exposure from 1984 till December 2, 2020. Other review studies included in their research a general target group or outcome measure and there is no previous study review, using 8-OHdG biomarker as oxidative stress indicator because of medical ionizing radiation. In this review, we hoped to find results that could show which study design and outcome measures should be used to measure the DNA damage due exposure to medical ionizing radiation.

There were many different methods for measuring results such as target population, analytical procedure, specimen types, measurement time, and factors that may affect the level of 8-OHdG, defined by all literatures. The quality of the studies also varied greatly and there was no agreement on the effective measures for the outcome. It was interesting only 10 studies were included in this review, but when reading the studies, we found that using 8-OHdG biomarkers is a difficult Several aspects need to be considered, such as identifying the target population, analytical methods, types of samples and time of measurement to determine the DNA effect of medical ionizing radiation. There were many conflicting variables, which may affect the levels of 8-OHdG and probably influence the findings.

8-OHdG measurement methods

We found that the target population ranged from patients with medical irradiation to staff with medical radiation exposure [6,11,12,14-19]. Other subject groups may also be included as potential target populations, or at least studied. For subjects other than those mentioned in the literature, such as nuclear medicine patients, fluoroscopy procedures patients, computed tomography patients and staff, the 8-OHdG level may be used as a radiation effect biomarker.

A variety of analytical methods for measuring 8-OHdG concentrations, such as ELISA, GC-MS, electrochemical detection with HPLC-ECD and tandem LC-MS/MS, can be used to evaluate 8-OHdG. The highly precise and sensitive techniques include GC-MS, HPLC-ECD and LC-MS/MS. For fast detection and quantification of 8-OHdG, ELISA kits have been established and are less expensive and time-consuming [19,20]. While ELISAs overestimate 8-OHdG levels, several studies have shown substantial positive correlations between 8-OHdG as calculated by ELISA and chromatographic methods. Consequently, chromatographic methods are preferred when accurate analysis is needed, but ELISAs can

be used adequately to compare 8-OHdG concentrations according to one study [20].

24-hour urine collection is commonly recommended. However, this is impractical in wide epidemiological researches. Thus, some studies have investigated the possibility of using spot morning urine samples. The first voided morning sample (on waking) is especially useful as it provides a time average for concentrations of biomarkers that may occur during sleeping hours (approximately 8 h). The (early) morning sample is also fairly free of the influence of dietary factors [21]. Most of the included studies in this scoping review mainly analyzed the 8-OHdG level by ELISA [10,11,13,16-18].

In recent years, 8-OHdG determination and analysis can be conducted as a biomarker of oxidative stress, ageing, and carcinogenesis in animal organs and human samples (urine, human organs, leukocyte DNA) [22]. In clinical practice, urine has long been considered a favored diagnostic biofluid compared to other biological matrices such as plasma, serum and saliva as it is sterile, easily obtainable in large quantities and non-invasive for patients. Therefore, the first option for disease risk assessment, early detection, care and prognosis should be urinary 8-OHdG study [23]. In general, there are some benefits of measuring urinary 8-OHdG, such as its high stability in urine. Results of urinary 8-OHdG samples reflect oxidative DNA damage and repair from all the cells in the organism [19,21]. Among the included studies in this scoping review, the percentage of studies that used urine samples [6,12-16,18] was higher than the studies that used blood samples [10,11,17].

8-OHdG as biomarker of oxidative DNA damage of exposure to medical ionizing radiation

8-OHdG research in human leukocyte DNA and in urine are new approaches to determine the cancer risk of a person due to oxidative stress. 8-OHdG is one of the primary forms of oxidative DNA damage and a valuable cellular oxidative stress marker [20]. Some studies measured 8-OHdG levels and correlated the change in the level compared to the amount of radiation dose exposure, recorded for each enrolled patient, and also compared 8-OHdG results with the control group [6,12,14,16]. Meanwhile, in another study, the 8-OHdG level was measured without measuring the amount of radiation, but the comparison was based on a control group [17]. Moreover, 8-OHdG level was measured and correlated to the change in the level compared to the amount of radiation dose exposure, recorded for each enrolled patient [13]. Other studies suggested measuring 8-OHdG level and correlated the change in the level compared to the amount of radiation dose exposure, recorded for each enrolled subject and also compared 8-OHdG results with a control group of non-radiation workers [10,11,15,18].

After four treatment sessions, serum 8-OHdG levels decreased, but increased significantly with radiotherapy with cumulative doses of 10, 20 and 30 Gray (Gy). It was surprising and regrettable that there was no substantial difference between the different therapeutic dose groups in serum 8-OHdG levels, and no linear association between 8-OHdG and accumulated exposure dose was observed [11]. This is consistent with what other research, which found that serum levels of 8-OHdG in patients, who have long been exposed to radiation due to radiotherapy, are lower than healthy subjects, and there is no relationship between collective dose and serum levels of 8-OHdG due to DNA repair capacity [15]. The findings should be viewed from many angles in order to prevent error and mitigate the accumulation of oxidative DNA damage caused by ionizing radiation because living organisms can have a series of defense mechanisms. DNA damage often takes time to repair; thus, adjustments in DNA adduct output, resulting from ionizing radiation may be more important in the recovery process (several days or

months) than in the initial damage period. In addition, the fact that 8-OHdG has been associated with numerous cancers, suggesting that patients typically have higher 8-OHdG levels than healthy individuals, which may be a confounding factor. Cancer cells are gradually destroyed by radiation therapy, resulting in a drop in serum 8-OHdG levels [11]. Patients were divided into two groups based on reaction to therapy in order to assess the changes in urinary 8-OHdG/creatinine in the radiotherapy group. During the course of radiotherapy, there was a rising trend in values (10 and 30 Gy). Urinary 8-OHdG/creatinine returned to the baseline level two months after radiotherapy. It is important to note that patients, who show resistance to radiation therapy, have more pronounced rise in their values than those who responded. The decrease in the mass of the tumor through radiation-induced necrosis is likely to affect these findings. Study results indicate that tumor necrosis is not responsible for a rise in urinary levels of 8-OHdG/creatinine [16].

Among interventional radiologists, serum 8-OHdG levels are higher than other radiation workers, suggesting a higher degree of oxidative DNA damage in the bodies of the former, for which radio intervention requires employees to maintain direct contact with X-rays for a long period of time [11]. Recent research showed that the elevated urinary levels of 8-OHdG, found among pilots, would last until exposure to cosmic radiation was over [24]. For radiography staff, there is a strong positive association between serum 8-OHdG levels and working period or personal effective dose ($P < 0.05$). This result showed that serum 8-OHdG levels rise due to an increase in the radiation exposure and working duration [11]. One study of X-ray irradiated mice showed a significant increase of 8-OHdG, which was observed at 0.2 Gy exposure and the levels appeared to increase linearly in a semi-logarithmic scale in the range of 0.2 to 5 Gy [25].

The findings of one study showed that levels of 8-OHdG in urine of individuals exposed to ionizing radiation were significantly higher than those who did not have exposure. The mean effective dose of radiation in the last one year and the last 5 years as well as the collective effective doses of radiation in the last one year and the last 5 years periods in the nuclear medicine group were significantly higher than the other groups [15]. In another study, in 18 of the 19 study participants, the urinary 8-OHdG levels after the procedure increased. Post-pre 8-OHdG was not significantly associated with body mass index, age, body surface area, and catheterization study length and fluoroscopy time. Cumulative air kerma was the variable that most strongly and significantly associated with post-pre 8-OHdG level ($R^2 = 0.7179$, $P = 0.0007$) during cardiac catheterization [6].

Confounding factors may influence 8-OHdG level

In the included studies, some factors are indicated, affecting the 8-OHdG level induced by exposure to ionizing radiation, and the 8-OHdG biomarker is considered as an unspecific marker because there are multiple confounding factors (e.g. gender, age, smoking, alcohol intake, diet, vitamin status, physical activity) that may influence the formation of 8-OHdG [5]. The underlying condition in patients with chronic synovitis undergoing radiation synovectomy should be considered when interpreting the levels of biomarkers of cytogenetic damage in terms of malignancy risk [14].

Many confounding factors, such as sex, age and smoking status, may influence the level of 8-OHdG [18]. One research indicates that there were no major variations in gender or smoking habits between the groups [16]. Meanwhile, the research conducted by Loft et al, described smoking, body mass index and sex as important determinants of 8-OHdG urinary excretion, and also described smoking as the most important factor in 8-OHdG urinary excretion [26]. Moreover, the level of serum

8-OHdG of radiation workers had no association with age, sex and occupation [11]. In both the control group and the group exposed to radiation, females had lower 8-OHdG than males, whereas smokers had higher 8-OHdG levels relative to non-smokers [18]. In another study, there were no major variations in age and biomarker levels between the groups [14].

8-OHdG levels are affected by working period and job classification. 8-OHdG levels were higher for seniority staff worked about 5, 10 and over 15 years than for those worked less than 5 years ($P<0.05$) [11]. Meanwhile, another study found that the nuclear medicine group had the highest urine concentration of 8-OHdG than the radiotherapy and radiology groups [15].

Gender was the most important determinant of 8-OHdG excretion in nonsmokers, while body mass index was the only significant predictor in smokers [5]. Regarding the diet effect on 8-OHDG level, Kim et al, concluded that the quality of diet may be useful in reducing oxidative stress [27]. The adverse health effects of ionizing irradiation may be greatly affected by the diet. Especially, nutrient deficiency may be a significant factor, increasing the risk of ionizing irradiation [25]. One research indicated that 8-OHdG level for patients receiving radiotherapy course is significantly higher in small cell carcinoma (SCC) patients relative to the non-SCC patients and the matched controls [16]. Earlier studies have shown that 8-OHdG is found in precancerous and cancerous tissues or cancer cell lines at high concentrations relative to neighboring normal tissues or normal cell lines [23]. 8-OHdG has been correlated with various tumors, suggesting that patients have usually elevated 8-OHdG levels compared to healthy individuals [11]. 8-OHdG to creatinine urinary excretion levels were found to be higher in small cell lung cancer patients than in controls [28]. In addition, stage and basic characteristics of cancer groups affected the range of excretion 8-OHdG [13]. The urinary 8-OHdG level steadily increased from stage I to IV, and the urinary 8-OHdG content in patients with tumor metastasis was significantly higher than in patients without tumor metastasis [23].

Conclusion

In conclusion, this scoping review shows that medical ionizing radiation and 8-OHdG concentrations have a strong positive relationship. In other words, there is a direct association between the radiation dose and 8-OHdG level of radiation workers, taking into account the lack of clarification of the relationship entirely for cancer patients receiving radiotherapy due to the multiple factors affecting it. Smoking has a strong impact on the 8-OHdG level, but there was no age influence demonstrated. Due to ionizing radiation from medical procedures for patients and staff, theoretically, 8-OHdG can be used to assess elevated oxidative stress. We suggest a late-term measurement of the 8-OHdG level. In addition, it would then be feasible to unify radiation dose and 8-OHdG level measurement methods, resulting in the comparison of values across studies.

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Conflict of Interest

None

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