*REVIEW*

# *Human DNA damage in arterial hypertension: a mini review*

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**ABSTRACT**

Introduction: Human DNA damage occurs in a wide range of diseases and has been the subject of intensive research in recent years. Arterial hypertension (AH) is diagnosed when repeated measurements for blood pressure in a doctor's office yield values of 140/90 mmHg or higher. Human DNA damage in AH has begun to be studied in recent years as it appears to be possibly related to the pathophysiology of the disease.

Aim: The aim of this mini review is to provide a short summary of the latest information on human DNA damage in AH.

Material and methods: A brief review was performed based on a narrative synthesis of previously published literature. The material of the present study was exclusively Internet-based. A comprehensive electronic literature search in the database PubMed using the following terms/key words: "DNA damage" AND "arterial hypertension" AND "humans".

Results: Numerous research studies have been conducted to analyze DNA damage in patients with AH. Two methods, the Comet assay and ELISA were utilized by researchers to assess the level of DNA damage in these individuals. The results from these studies consistently demonstrated higher levels of DNA damage in hypertensive patients compared to normotensive controls. Additionally, a positive correlation between DNA damage and blood pressure was observed. Furthermore, an association between oxidative stress and AH was indicated by higher levels of the oxidative stress marker 8-OHdG in hypertensive individuals.

Conclusions: In AH, there is an increase in human DNA damage in blood or urine compared to healthy individuals. The findings were consistent in multiple case-control studies, suggesting a potential association. Further research with larger sample sizes and diverse populations is needed to confirm these observations and explore the underlying mechanisms for potential therapeutic strategies.

*Keywords:* DNA damage, arterial hypertension, human biology

**I. Delimaris. Human DNA damage in arterial hypertension: a mini review. Scientific Chronicles 2025; 30(1): 17-28**

## INTRODUCTION

Alterations in human DNA are divided into two categories: mutations (change of bases in both DNA chains, which cannot be recognized and cannot be repaired) and DNA damage (alterations in the DNA structure, which are recognized by special enzymes and

can be repaired) [1,2]. The types of DNA damage based on the cause of the damage are divided into endogenous and exogenous. Endogenous damage is caused during cell metabolism (mainly replication), while exogenous damage is caused by ultraviolet (UV) radiation, thermal decomposition of substances, toxins, smoking and various chemical mutagens. The categories of DNA damage based on the chemical mechanism are: a) errors ("typing errors") of the DNA polymerase during replication (mismatch of bases), b) alterations of bases (oxidations, methylations, depurinations, deaminations), c) DNA breaks (ss break: break of one DNA chain, ds break: break of both DNA chains), d) pyrimidine dimers and addition of bulky chemical molecules (bulk adducts) (Figure 1) [3,4].

The comet assay, also known as the single-cell gel electrophoresis assay, is a commonly used visual technique for measuring DNA damage. Under alkaline conditions, DNA molecules with varying molecular weights and electric charges behave differently in an electric field. Undamaged DNAs migrate during electrophoresis without losing their integrity, while denatured DNA fragments move out of the damaged DNAs' cell nuclei. An increased migration of genetic material from the nucleus known as the "comet head" to the tail is known as "comet damage". Comet assay is essentially a light microscope quantification of the obtained images [5]. Moreover, human 8-hydroxy-2-deoxyguanosine (8-OHdG) ELISA (Enzyme-Linked Immunosorbent Assay) is an accurate in vitro quantitative method for detecting 8-OHdG in human saliva, serum, urine and plasma sample .8-OHdG is a modified base in the DNA as a result of an attack by hydroxyl radicals.

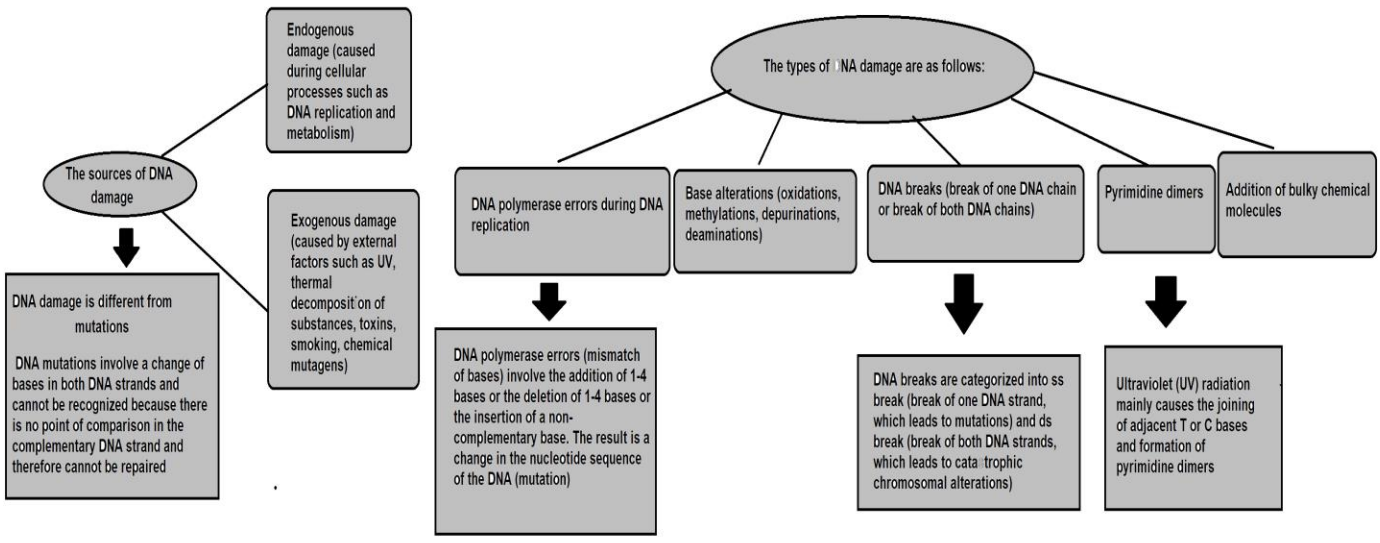


**Figure 1**: Diagram showing the sources and the types of DNA damage.

The determination of 8-OHdG levels using ELISA is becoming increasingly popular as a stable, sensitive and an integral marker for oxidative damage of DNA [6].

In 2019, the global age-standardized prevalence of arterial hypertension in adults aged 30–79 years was 33% [7]. Arterial hypertension (AH) is diagnosed when repeated measurements for blood pressure in a doctor's office yield values of 140/90 mmHg or higher. The diagnosis should be confirmed by 24-hour ambulatory blood pressure monitoring or by home measurement. Further risk factors and end-organ damage should be considered as well. According to the current European guidelines, the target blood pressure for all patients, including those with diabetes mellitus or renal failure, is <140/90 mmHg. If the treatment is well tolerated, further lowering of blood pressure, with a defined lower limit, is recommended for most patients [8].

Essential, primary, or idiopathic hypertension is defined as high blood pressure in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension or mendelian forms (monogenic) are not present. Essential hypertension accounts for 95% of all cases of hypertension. It has frequently been indicated that the causes of essential hypertension are not known. A number of known etiological factors increase blood pressure, including obesity, insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), aging and perhaps sedentary lifestyle, stress, low potassium intake, and low calcium intake. Furthermore, many of these factors are additive, such as obesity and alcohol intake [9].

From a pathophysiological point of view elevated blood pressure can be caused by increased cardiac output, increased peripheral resistances of the arterial tree, or a combination of both. Factors such as chemicals secreted by the kidney and brain, increased sympathetic nervous system activity, and activation of the renin-angiotensin-aldosterone axis can contribute to hypertension. In elderly individuals, increased peripheral resistances and arterial stiffness often lead to isolated systolic hypertension. Secondary hypertension is more common in young individuals, with causes including renal diseases, renal vascular hypertension, and primary aldosteronism. Various medications and substances can also lead to an increase in blood pressure. Lifestyle modifications, such as a healthy diet, regular exercise, and medication, are usually enough to manage high blood pressure and reduce its risks [10,11].

Human DNA damage in arterial hypertension has begun to be studied in recent years as it appears to be possibly related to the pathophysiology of the disease [12,13]. The aim of this mini review is to provide a short summary of the latest information on human DNA damage in arterial hypertension via a clinicobiological approach. Mini reviews offer a rapid means of disseminating emerging evidence, facilitating the timely communication of new findings to shape future research. They provide flexibility in addressing a broad array of research questions, enabling exploration of diverse topics without the constraints of strict inclusion criteria. They also aid in identifying gaps in current knowledge and proposing future research directions. Additionally, by stimulating critical

thinking through the presentation of multiple perspectives, mini reviews can inspire new insights and discoveries in the field [14]. The relevance and significance of this brief narrative review to the field of cardiology lie in its investigation of the relationship between DNA damage and arterial hypertension. Understanding the potential mechanisms by which DNA damage contributes to the pathophysiology of hypertension can provide valuable insights into the development and progression of this cardiovascular disease. This mini review of the current literature on human DNA damage in arterial hypertension contributes to a deeper clinicobiological understanding of the disease, ultimately aiding in the development of research approaches in cardiology.

## MATERIAL AND METHODS

### Design

A brief review was performed based on a narrative synthesis of previously published literature.The material of the present study was exclusively Internet-based. A comprehensive electronic literature search in the database PubMed was performed (from 10 February 2024 to 30 March 2024) using the following terms/key words: "DNA damage" AND "arterial hypertension" AND "humans". In addition, a search in the reference lists was carried out.

Criteria for inclusion of studies were:

- Literature written in English.
- Literature published from January 2000 to March 2024
- Studies that involved men and women with hypertension.
- Studies that had keywords in the title and/or abstract

Criteria for exclusion of studies were:

- Reviews
- Conference papers
- Book chapters
- Books
- Short surveys
- Articles and documents written in languages other than English

The search process is shown in Figure 2.

### Selection of studies

All references obtained from the search were organized and duplicates were excluded. The titles and abstracts were screened for content and relevance to the topic with focus on the inclusion criteria. The integral text of selected titles was read, and the reference list of selected articles was consulted in order to find out other relevant publications. Additionally, studies which failed to adequately describe human DNA damage in arterial hypertension were excluded.

### Data extraction and analysis

The essential data from each published study were extracted and synthesized. The results are presented in a brief narrative form.

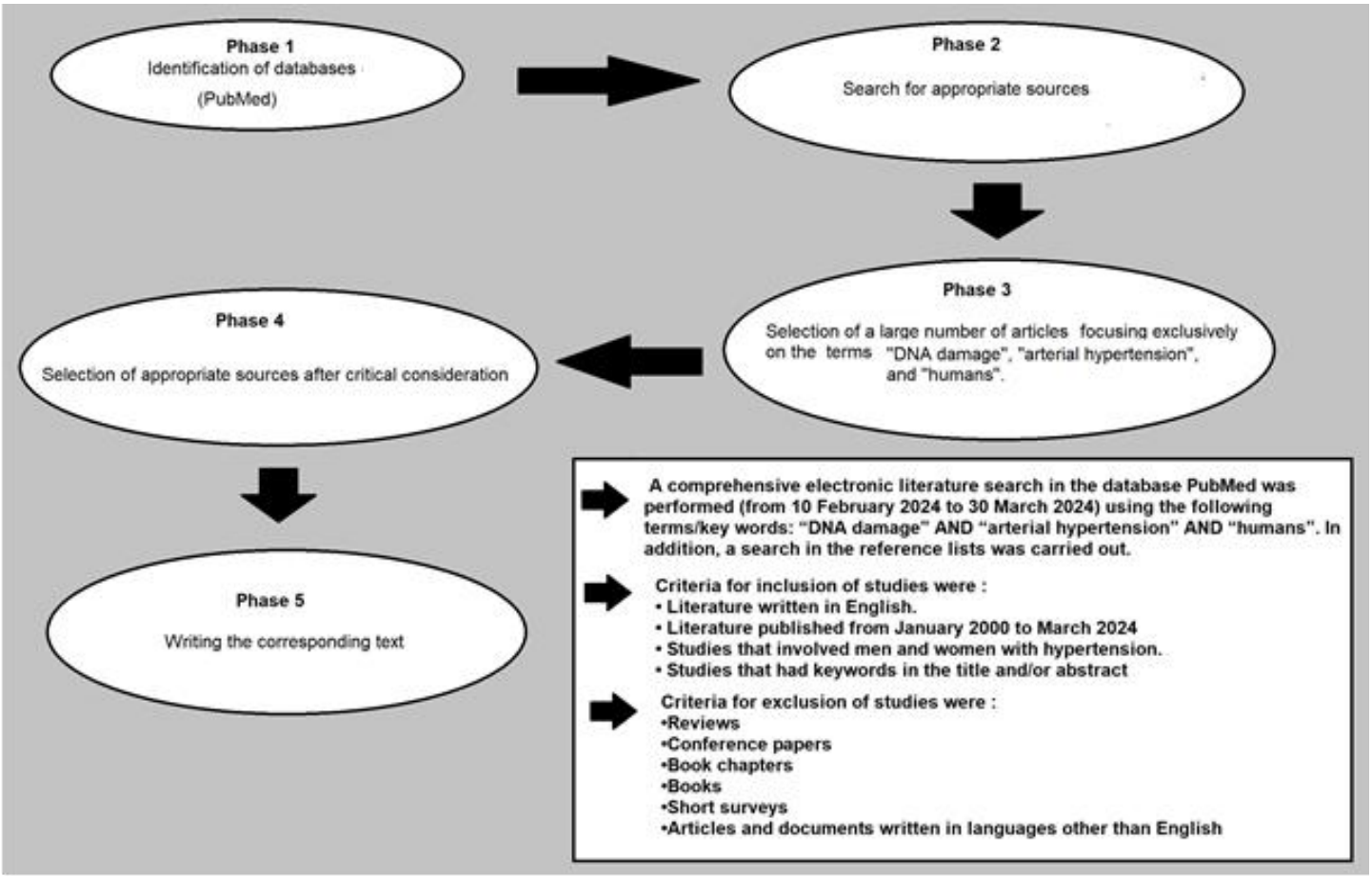


**Figure 2**: Flow chart demonstrating the search strategy of the brief narrative review.

**DNA damage estimation in arterial hypertension using Comet assay**

Yildiz *et al* [15] evaluated the damage to lymphocyte DNA in patients suffering from sustained hypertension (SHT) and white-coat hypertension (WCH). The study comprised 19 age- and sex-matched healthy volunteers as controls, 23 patients with WCH, and 21 patients with recently diagnosed SHT. Office blood pressure measurements, an echocardiogram, and 24-hour ambulatory blood pressure monitoring were performed on each subject. The alkaline comet assay was utilized to evaluate DNA damage in peripheral lymphocytes. Significantly higher lymphocyte DNA damage ($p<0.001$) was observed in SHT patients compared to the WCH and control groups [15].

Gür *et al* [13] examined the damage to lymphocyte DNA in individuals suffering from both non-dipper hypertension (NDH) and dipper hypertension (DH). The study included twenty (20) healthy volunteers (control group), thirty-three (33) patients with NDH (NDH group), and thirty-one (31) patients with DH (DH group) (64 hypertensive patients in total). The comet assay was used to measure DNA damage in peripheral lymphocytes. The NDH group had a mean DNA damage value greater than the DH and control groups ($P=0.002$ and $P<0.001$, respectively). The DH group's mean DNA damage value was higher ($P<0.001$) than the control groups [13].

The degree of oxidative DNA damage in total lymphocytes using the commet assay and its relationship to essential hypertension were examined by Subash and co-authors [16]. For the study, a total of 130 subjects were chosen. Of the hypertensive subjects under investigation, thirty (30) had just received their diagnosis, fifty (50) were already receiving medication for their hypertension, and the remaining fifty (50) were normotensive controls. When comparing the control group to the hypertensive patients (both newly diagnosed and already on medication therapy), there was a significant increase in DNA damage in lymphocytes ($p< 0.05$). When comparing newly diagnosed hypertensive patients to those who were already receiving medication therapy, there was a significant increase in DNA damage ($p< 0.05$) [16].

Saiedullah *et al* [17] measured the extent of DNA damage in peripheral lymphocytes obtained from 40 normotensive and 46 hypertensive subjects. DNA damage was higher in hypertensives than normotensives ($p< 0.05$) and DNA damage correlated positively with blood pressure ($p < 0.05$) [17].

Subash and co-authors [18] investigated the extent of oxidative DNA damage in peripheral lymphocytes using the comet assay and its relationship with essential hypertension (EHT). A total of 100 subjects were included for the study. Of these 50 were normotensive controls (group-1), 50 were newly diagnosed (group-2) and were not on any antihypertensive drugs, and 50 were newly diagnosed essential hypertensive patients that underwent drug therapy for 1 year and considered as group-3 (total number of hypertensive subjects N=100). Lymphocyte DNA damage was significantly increased in newly diagnosed hypertensive patients compared with control group ($p<0.05$). The major decrease in DNA damage was observed after 1 year of antihypertensive therapy in treated group compared with newly diagnosed hypertensive patients ($p<0.05$) [18].

Gur *et al* [19] examined the relationship between various left ventricle (LV) geometric patterns and damage to the DNA of lymphocytes in hypertensive patients. They looked at 24 healthy control subjects and 84 hypertensive patients. In patients, four distinct geometric patterns were found based on relative wall thickness and LV mass index. All subjects had peripheral lymphocyte DNA damage determined using the comet assay. Compared to the control group, hypertensive patients had higher levels of DNA damage ($p=0.001$). When compared to all other geometric patterns, the concentric hypertrophic geometric pattern showed the largest increase in DNA damage ($p<0.001$, for all) [19].

**DNA damage estimation in arterial hypertension using 8-hydroxy-2'-deoxyguanosine (8-OHdG)/ELISA**

Negishi *et al* [20] used ELISA to measure 8OHdG in urine from sixty (60) individuals (n = 22 normotensives and n = 38 hypertensives). After adjusting for age and gender, the 24-hour urinary 8-OHdG of the hypertensive individuals (SBP > or = 140 mmHg and/or DBP > or = 90 mmHg) was significantly higher than that of the normotensive individuals (SBP <140 mmHg and DBP <90 mmHg) [20].

In a case-control study performed by Negishi *et al* [21] sixty (60) subjects were divided into two groups, hypertensive subjects (n=38, systolic blood pressure (SBP) > or = 140 mmHg and/or diastolic blood pressure (DBP) > or =90 mmHg) and normotensive subjects (n=22, SBP < 140 mmHg and DBP < 90 mmHg). The mean levels of 8-OHdG in urine using ELISA were significantly higher in the hypertensive subjects than in the normotensive subjects ($P < 0.05$) [21].

Urinary DNA estimation as a marker to predict the degree of cellular oxidative stress in essential hypertension was assessed by Subash and co-authors [22]. For the study, 180 participants in total were chosen. Of the hypertensive subjects under investigation, thirty (30) had just received their diagnosis and were not taking any antihypertensive medications. The other seventy-five (75) hypertensive patients had already been on medication for a year, and the remaining seventy-five (75) were normotensive healthy controls with blood pressure ≤ 120/80 mmHg. Using ELISA, the 8-OHdG level in urine was significantly higher in hypertensive patients (both newly diagnosed and already on medication therapy) than in the control group ($p<0.05$). When comparing hypertensive patients who were already receiving medication therapy to those who had just received a diagnosis, a significant increase in 8-OHdG was found ($p<0.05$) [22].

Acording to Kotani *et al* [23] oxidative stress, measured by 8-OHdG, is linked to arterial stiffness in type 2 diabetes and hypertension. In a study of 76 patients (patients with type 2 diabetes mellitus (T2DM): a) without hypertension, n=31, b) with hypertension, n=45), those with both conditions had higher pulse wave velocity (PWV) compared to those without hypertension (1,597 cm/s vs 1,442 cm/s). 8-OHdG levels correlated positively with PWV in hypertensive patients with T2DM ($r = 0.33$, $p < 0.05$) [23].

In a study of Yıldırım *et al* [24] participants were allocated into 3 groups: 40 healthy controls, 36 patients with white coat hypertension (WCH), and 40 patients with sustained hypertension (HT). The levels of oxidative stress markers such as 8-OHdG were compared between patients with white coat hypertension, sustained hypertension, and normotensives. Results showed that patients with sustained hypertension had significantly higher levels of 8-OHdG compared to those with white coat hypertension and normotensives ($p<0.001$). This suggests that DNA damage is more pronounced in patients with sustained hypertension [24].

## DISCUSSION

The studies conducted by Yildiz et al. [15], Gur *et al* 13], Subash *et al* [16], Saiedullah *et al* [17], and Kotani *et al* [23] all focused on evaluating DNA damage in patients with arterial hypertension using different methods such as the Comet assay and ELISA. Yildiz and colleagues [15] found significantly higher levels of DNA damage in peripheral lymphocytes of patients with sustained hypertension compared to those with white-coat hypertension and healthy controls. Similarly, Gur *et al* [13] reported higher DNA damage in individuals with non-dipper hypertension compared to those with dipper hypertension and normotensive controls. Saiedullah *et al* [17] also observed increased

DNA damage in hypertensive subjects compared to normotensive individuals, with a positive correlation between DNA damage and blood pressure. Subash and colleagues [16] found a significant increase in DNA damage in hypertensive patients compared to normotensive controls, and a decrease in DNA damage after one year of antihypertensive therapy. Furthermore, Negishi *et al* [21] and Subash *et al* [22] reported higher levels of the oxidative stress marker 8-OHdG in hypertensive individuals compared to normotensive controls, indicating a relationship between oxidative stress and hypertension. Overall, these findings suggest a potential association between oxidative DNA damage and essential hypertension. The mechanism through which DNA damage might occur in individuals with arterial hypertension is oxidative stress (Figure 3). Elevated levels of reactive oxygen species (ROS) can lead to the formation of DNA adducts and strand breaks, as evidenced by the increased levels of oxidative DNA damage markers, such as 8-hydroxy-2'-deoxyguanosine (8-OhdG) [20,22].

The strengths of the above studies include the utilization of well-established methodologies such as the comet assay and ELISA to assess DNA damage and oxidative stress markers in hypertensive patients. The studies involved appropriate control groups to compare the levels of DNA damage and oxidative stress markers, providing a comprehensive evaluation of the impact of hypertension on cellular damage. The inclusion of a significant number of subjects in each study increased the robustness and reliability of the findings. The findings from these studies suggest a clear association between hypertension and increased DNA damage, highlighting the potential role of oxidative stress in the pathogenesis of essential hypertension. Additionally, the correlation between DNA damage and blood pressure levels in hypertensive patients further strengthens the evidence for the involvement of oxidative stress in the development and progression of hypertension.

Overall, methodological rigor, appropriate study designs, and consistent findings across multiple studies contribute to the strengths of the research on DNA damage estimation in arterial hypertension using Comet assay and 8-hydroxy-2'-deoxyguanosine (8-OhdG)/ELISA [12-24].

The limitations of the above studies include small sample sizes, which may not provide a comprehensive understanding of the relationship between DNA damage and hypertension. Additionally, the cross-sectional design of the studies limits the ability to establish causality between DNA damage and hypertension. The lack of long-term follow-up in some studies may also prevent the assessment of changes in DNA damage over time. Furthermore, the variability in measurement techniques and inconsistencies in the definition and classification of hypertension across studies may lead to potential bias and confounding factors. The reliance on certain biomarkers, such as 8-OHdG and total antioxidant status, as indicators of DNA damage and oxidative stress may not fully capture the complexity of these mechanisms in hypertensive patients. Overall, these limitations highlight the need for larger, longitudinal studies with standardized methodologies to better elucidate the relationship between DNA damage and arterial hypertension [12-24].

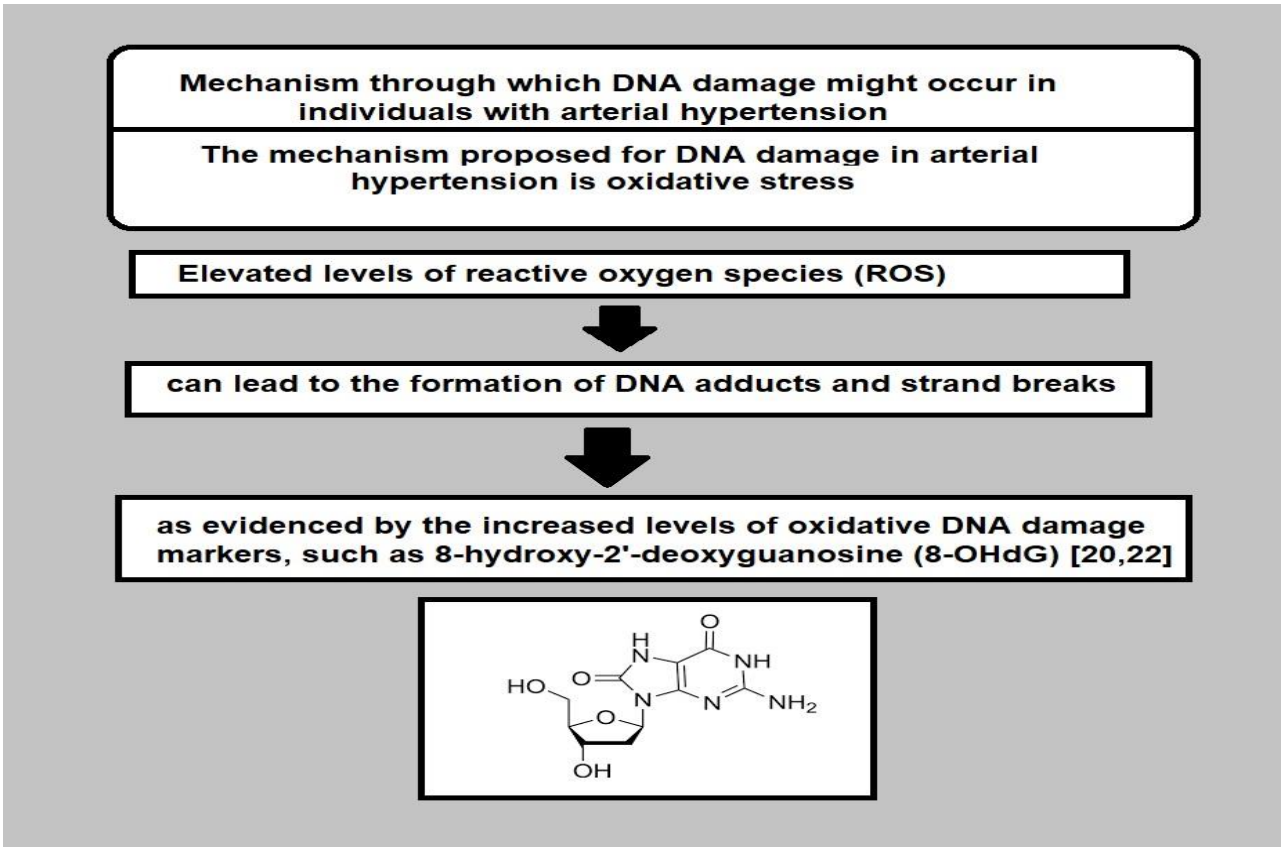


**Figure 3**: Mechanism through which DNA damage might occur in individuals with arterial hypertension [20,22].

Future directions in the above studies could focus on exploring the underlying mechanisms that lead to DNA damage in hypertensive patients. Understanding the specific pathways involved in oxidative stress and DNA damage could provide potential targets for intervention strategies aimed at reducing cardiovascular risk in this population. Additionally, investigating the relationship between DNA damage and other biomarkers of cardiovascular disease could offer a more comprehensive understanding of the pathophysiology of hypertension. Longitudinal studies following hypertensive patients over time could help elucidate the progression of DNA damage and its impact on cardiovascular outcomes. Furthermore, exploring the potential role of lifestyle interventions, such as diet and exercise, in reducing DNA damage in hypertensive patients could provide valuable insight into the development of personalized treatment approaches for this population. Overall, future research in this area has the potential to inform clinical practice and improve the management of arterial hypertension [12-24].

## CONCLUSIONS

In conclusion, the results of this mini review indicate that there is a notable increase in human DNA damage, as determined by comet assay in blood or 8OHdG levels in blood

or urine, in individuals with arterial hypertension when compared to those without the condition. These findings were consistent across multiple case-control studies. However, it is important to note that further research is required to confirm these observations, especially with larger sample sizes that include a more diverse population of patients. Additional studies should be conducted to explore the underlying mechanisms behind the observed increase in DNA damage in individuals with arterial hypertension. Understanding the relationship between hypertension and DNA damage may provide valuable insights into potential therapeutic strategies for preventing and managing the condition. Overall, the current evidence suggests a potential association between arterial hypertension and increased levels of DNA damage in humans, highlighting the need for further investigation in this area.

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