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Association Between Serum Paraoxonase-1 Activity and p53 Protein Levels in Smoking Patients with Hypertension

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ABSTRACT: **Background**: Smoking is a major driver of genetic instability and physiological alterations that escalate cardiovascular risk and cancer. Smoking a source of oxidative stress and a well-known risk factor for hypertension.

The Aim : to evaluate oxidative stress and DNA damage by quantifying 8-OHdG and TP53 levels, with the activity of the antioxidant enzyme PON-1, in smokers, and to examine the influence of hypertension and amlodipine treatment on these parameters.

Method: A total of 177 participant were recruited and divided into three groups: (1) hypertensive smokers group, (2) normotensive smokers group and (3) a control group. The ages of participants ranged between (26-64) years. Serum 8-OHdG ,TP53 levels were measured using ELISA technique, and the PON-1 activity were measure by using standard laboratory methods.

Results: Statistical analysis revealed a substantial elevation ($p < 0.001$) in 8-OHdG and TP53 levels among smokers relative to the control group. The group of smokers with hypertension exhibited the highest levels (140.60 ng/ml and 5534.2 pg/ml, respectively). PON-1 enzyme activity was markedly diminished in smokers, particularly in those with hypertension (4.07 kJ/L), compared to smokers with normal blood pressure (6.02 kJ/L) and healthy individuals (9.67 kJ/L).

Conclusion: Smoking causes severe depletion of the antioxidant defense system (PON-1) and increase gene damage (8-OHdG, TP53). Although patients were receiving amlodipine treatment, this treatment was insufficient to reverse the observed genetic damage and oxidative stress.

INTRODUCTION:

Hypertension (HTN) is a prevalent condition, and its incidence has markedly risen in recent decades. Hypertension is a covert, yet often overlooked peril to world health. It acts as a principal risk factor for cardiovascular illnesses (CVDs). Smoking has become the most overlooked cause of death worldwide. Comprehensive studies have associated smoking with heightened inflammation, endothelial cell dysfunction, and modifications in hypertension regulation, collectively resulting in a 39% rise in male smoking prevalence and a 45% rise in female smoking rates, with of based on gender and age. Hypertension is an escalating global health issue, especially in Middle Eastern nations(1)

Tobacco smoke (TS) comprises a multitude of chemicals, including aldehydes, which have been demonstrated to directly interact with naked DNA and cellular genomic DNA, resulting in various isomeric forms of DNA adducts. Additionally, TS contains numerous compounds such as polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines (AAs),

nitrosamines, and benzene, which, through metabolic activation, can be converted into derivatives capable of covalently bonding with naked DNA and cellular genomic DNA, thereby forming distinct isomeric forms of DNA adducts.(2)

The World Health Organization (WHO) categorizes smoking as a chronic, progressive disease that is also 'contagious'; additionally, smoking can harm every area of the body [2].

The predominant form of smoking is via cigarettes; additional smoking devices encompass pipes, cigars, bidis, narghile, vaporizers, and bongs.The predominant material smoked is tobacco, a plant belonging to the genus Nicotiana within the Solanaceae family (3). Smoking is recognized as a significant contributor to oxidative stress, which subsequently induces DNA damage and mutations in tumor-associated genes, factors implicated in carcinogenesis. The oxidative damage to DNA by reactive oxygen and nitrogen species results in the formation of 8-hydroxy-2-deoxyguanosine (8-OHdG), a specific biomarker of oxidative stress. Elevated levels of 8-OHdG correlate with the aging process and various pathological conditions, including cancer, diabetes, and hypertension.(4)

Oxidative stress is now well established as an outcome of the imbalance between free radical production and their scavenging mechanisms, favoring the former. The dysfunction of antioxidant defense mechanisms contributes to the pathophysiology of various metabolic disorders, including atherosclerosis. The concept posits that PON1 is the HDL component accountable for its antioxidant properties, and consequently, its antiatherogenic effects. Cigarette smoke contains several reactive chemicals and heavy metals that adversely affect PON1 (5).

Paraoxonase (PON) refers to a family of polymorphic enzymes—PON1, PON2, and PON3—that demonstrate arylesterase activity and are present in human serum. The paraoxonases facilitate the hydrolysis of aromatic carboxylic acid esters and organophosphates, such as the active metabolite paraoxon. Paraoxonases are glycoproteins composed of roughly 337 amino acid residues, with a molecular mass of about 43 KDa. The genes that encode paraoxanase are situated inside a cluster on a chromosome.
Numerous signs of oxidative stress, such as paraoxonase -1 (PON1) and 8-hydroxy-2-deoxyguanosine (8-OHdG). The enzyme mitigates oxidative damage. PON1 is an essential endogenous scavenger of free radicals in the human body.(6).

The tumor suppressor protein p53 is a significant transcription factor that regulates various cellular metabolism and functions. It is termed the "guardian of the genome" due to its crucial role in responding to DNA damage and its interaction with multiple signaling transduction and amplification pathways related to responses to abnormal propagation signals, DNA damage, hypoxia, and osmotic stress. Mutations in p53 are frequently observed in numerous cancer types and serve as an additional cause and risk factor for tumor progression, chemotherapy resistance, and poor prognosis.(7)

This study aim to investigate the synergistic impact of smoking and chronic hypertension on oxidative DNA damage ,antioxidant defense ,and gentic stability.specifically, we sought to evaluate the levels of 8-hydroxy-2´deoxyguanosine (8-OHdG) and enzymatic activity of paraoxanase-1(PON1),alongside the expression profile of TP53 gene.Furthermore,this research intends to explore the potential correlation between these molecular parameters to provide a deeper understanding of the pathophysiological mechanisms underlying vascular complications in hypertensive smokers

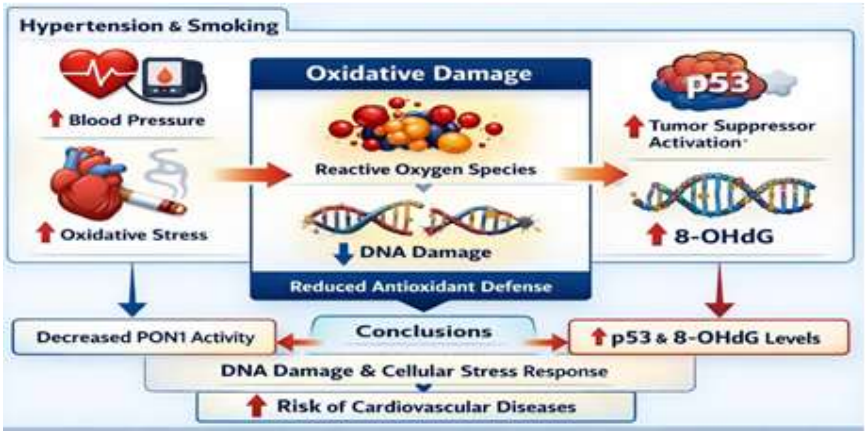


Figure 1: Association of PON1 activity, p53 & 8-OHdG Levels in hypertension

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MATERIAL AND METHODS

Study design

The present study included a total of 177 Iraqi participant aged ranged between (26-64) years, divided into three main groups : 62 healthy subjects, 72 smoker group without hypertension who were not receiving

any medicine, and 43 smoker with hypertension undergoing treatment with Amlodipine (10mg). Participants were recruited from Al-Yarmouk Teaching Hospital and the Baghdad Teaching Hospital over the period November 2024 to March 2025. The

study protocol was approved by the Ethics Committee of the College of Science/ University of Baghdad. The consent of all patients was taken and they were informed that the samples were for research purposes. Ref.: (Ref.CSEC/0325/0054).

All participants completed a structured questionnaire that included demographic data (age and sex), anthropometric measurements , and life style information . Clinical data

included measure blood pressure, medical history, and current medication use . Smoking habits were documented based on the type of smoking (cigarette, argil, or vaping) and frequency. A sample collected by taken 10 ml of venous blood from each participants. Blood samples were collected and placed in gel tubes and allowed to clots for 20 min ,followed by centrifugation at 3000 rpm for 10 min to obtain serum. The serum was separate and put it into an Eppendorf tube and stored at -20 c until analysis.

Exclusion criteria:

Participants have rheumatoid arthritis, acute or chronic inflammatory conditions, chronic disease such as diabetes mellitus or cardiovascular disease, liver cirrhosis, malignant tumors, in the study were excluded.

Biochemical assay:

Blood pressure was measured by using a Rossmax electronic blood pressure monitor (Microcomputer- controlled , intelligent).

The concentration of 8-hydroxy-2'- deoxyguanosine (8-OHdG) was assessed by a Human 8-OHdG ELISA kit (Elabscience, catalogue No. E-EL- 0028, China), based on enzyme-linked immunosorbent assay. Absorbance was measured at 450 nm using a HumaReader HS (Human Diagnostics Worldwide, Germany), and concentrations were calculated from a standard calibration curve.

Paraoxanase (PON1) activity Were used a biochemical method in lab(Serum arylesterase activity was measured using a phenylacetate substrate the generration rate of phenol was determined at 270 nm and 25 c̊ for 2 min in the kinetic mode using UV –visible spectrophotometer by equation (8).

$$\text{Arylesterase activity (u/l)} = \frac{\Delta A/MIN \times Vt \times 10^6}{\varepsilon \quad vs}$$

Serum TP53 concentrations were quantified employing a commercially available sandwich ELISA kit (Elabscience, Wuhan, China; catalog No. E-EL-H0910), adhering to the manufacturer's specified protocol. Absorbance was then assessed at 450 nm utilizing a HumaReader HS microplate reader (Human Diagnostics Worldwide, Germany). Concentrations were calculated from a standard calibration curve and reported in Pg/mL

Statistical analyses:

The statistical analysis was conducted using IBM SPSS Statistics 26.0.One-way ANOVA was conducted to compare differences by age and differences in oxidative stress parameters, and then post-hoc HSD test .Moreover receiver operating characteristic (ROC) curve analysis was carried out to estimate the sensitivity and specificity of the diagnostic parameter. A P-value of 0.05 or less was a statistically significant value.Also ,risk was analyzed using logistic regression analysis.Evaluation ,computation of Odd Ratio (OR) and the 95% confidence interval (Cl).

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Result:

Demographic, Clinical, and Smoking Characteristics

The demographic and clinical characteristics of the three study groups are summarized in Table 1. The groups included healthy controls, normotensive smokers, and hypertensive smokers. No statistically significant differences were observed in age or body mass index (BMI) among the three groups ($p > 0.05$), indicating that the groups were well matched for these baseline characteristics. In contrast, smoking patterns differed significantly between groups ($p = 0.025$). Hypertensive smokers showed a higher prevalence of cigarette and narghile smoking, whereas vape use was least frequent in this group. Additionally, the duration of smoking was significantly longer in hypertensive smokers compared with normotensive smokers ($p = 0.014$).Blood pressure parameters showed significant group differences. Both systolic and diastolic blood pressures were markedly elevated in hypertensive smokers compared with controls and normotensive smokers ($p <0.001$). Whereas no significant difference was observed between controls and normotensive smokers. Overall, the finding indicate that age and BMI were comparable among the groups , while type of smoking, intensity smoking and blood pressure significantly differed among hypertensive smokers.

Table (1): Demographic, clinical, and smoking characteristics of control subjects, normotensive smokers, and hypertensive smokers value presented

Parameters	**Controls (N=62)**	**Normotensive smokers (N=72)**	**Hypertensive smokers (N=43)**	**F/X²**	***p*-value**
	(Mean ± SD)				
Age (year)	41.000±10.81347	40.1169±10.21476	42.5714±11.38708	0.715	0.49
BMI (kg.m^{-2})	5.4113±28.5767	28.5025±5.11363	30.0123±4.7593	1.332	0.267
Type of smoking Cigarette N(%) Narghile N(%) Vape N(%	---	40 (46.3%) 20 (26.1%) 12 (13.6%)	27 (62.8%) 15 (34.9%) 1 (2.3%)		0.025
Duration(year)	---	10.08±7.98	9.86 ± 8.02	24.959	< 0.001
SBP (mmHg)	138.60 ± 18.46	119.03 ± 18.47	138.60 ± 18.46	19.608	< 0.001
DBP (mmHg)	89.30 ± 12.03	76.66 ± 12.53	89.30 ± 12.03	17.661	< 0.001
Sex(male/female)	35 / 27	54/39	43/10	6.747	0.034

"Means in the same row with different superscripts (a, b) are significantly different ($p<0.05$)"

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The physiological and biochemical characteristics of study group are presented In the table 2.A comparative analysis was conducted to evaluate the variations in serum levels of (8-OHdG),Paraoxanase(PON-1),and Tumor protein TP53 across the three group:controls,normotensive smokers ,Hypertensive smokers. Statistical significance was determined using one-way ANOVA,indicating significant differences (p<0.05)between the groups.

Table 2: Comparison of serum 8-OHdG ,PON-1 and TP53 levels among control,normotensive smoker,and Hypertension smoker groups.

parameters	Control	Normotensive smoker	Hypertensive smoker	F/X²	*P*-value
	(Mean ± SD)				
8-OHdG (ng/ml)	59.08 ± 22.65	129.38 ± 20.27	140.60 ± 13.99	228.902	<0.001
PON-1 Ku/l	9.67[a] 4.77	6.01[b] ± 2.83	4.07[c] ± 2.17	37.020	<0.001
TP53 (pg/ml)	3024.10a±230.77	4791.2b±394.9	5534.2c±348.9	7.761	<0.001

"Means in the same row with different superscripts (a, b) are significantly different (p<0.05)"

Table No. 3 reviews the levels of some biochemical indicators associated with oxidative stress, genetic damage, and enzymatic activity in the serum of a sample of users of various types of tobacco products and electronic alternatives (cigarettes, hookah, and vape). These indicators were measured to assess the different biological effects of each type of smoking, including the measurement of 8-hydroxy-2'-deoxyguanosine (8-OHdG) as an indicator of DNA damage, TP53 protein associated with the cellular response to damage, and paraoxonase-1 (PON-1) enzyme, known for its antioxidant role.

Table 3: comparsion of serum 8-OHdG , TP53 and PON-1 among type of smokers

parameter	cigarette	narghil	vape	p-value
	(Mean ± SD)			
8-OHdG (ng/ml)	132.53 ± 8.72	125.96 ±25.40	132.37± 9.68	0.195
TP53(pg /ml	4374.30± 416.47	5294.28 ± 401.93	5278.76 ± 322.69	0.547
PON-1 (ku/L)	5.36 [a] ± 2.73	5.84 [a] ± 2.31	8.12 [b]± 2.98	0.001

To further elicidate the protective role of antioxidant enzyme ,table 4 have details the specific correlation between paraoxanase-1 (PON-1) activity and comprehensive set of parameters, including BMI ,Age,blood pressure.this focused correlation analysis is essential for understanding how systemic physiological changes in smoker modulate the activity of PON-1 as a primary defense mechanism .

Table4: Correlation matrix of PON-1,Tp53,and 8-OHdG in normotensive smoker participants

Parameter	**r**	**p-value**
Age(year)	0.006	0.956
BMI(Kg/m²)	-0.031	0.768

SBP(mmhg)	-0.187	0.074
DBP(mmHg)	-0.151	0.151
Smoking duration(year)	-0.065	0.539
PON 1	---	---
8-OHdG	-0.036	0.730
TP53	-0.106	0.314

The table 5 presents the correlation analysis of parameters within the hypertensive smoker group . this table explores the association between PON-1 ,8-OHdG ,and TP53 in patients concurrently exposed to the oxidative damage caused by smoking and the stress on the heart caused by high blood pressure. In addition, these correlations show the biochemical status of patients who are taking Amlodipine, which helps us understand how well blood pressure control works to reduce oxidative DNA damage and changes in proteins in this high-risk group.

Table 5: : Correlation of parameters in hypertension smoker participants PON-1 with 8-OHdG and TP53

parameters	r	p-value
Age (year)	-0.243	0.116
BMI(kg/M^2)	-0.112	0.478
SBP(mmHg)	-0.182	0.244
DBP(mmHg)	-0.181	0.245
Smoking duration	-0.087	0.584
PON 1	----	-----
8-OHdG	0.031	0.844
TP53	0.200	0.198

Table (6) displays the findings of receiver operating characteristic (ROC) analysis assessing the diagnostic efficacy of TP53, 8-OHdG, and PON1 in forecasting hypertension in smokers. The study encompasses the computation of the area under the curve (AUC), standard error (SE), and p-value, in addition to identifying the cut-off value that optimally balances sensitivity and specificity for these biomarkers as prospective diagnostic instruments.

Table 6: ROC analysis for the diagnosis of hypertension in the smoker group

Parameters	AUC	Cut -off	Sensitivity %	Specificity %	Youden Index	P-value
8-OHdG	0.999	92.882	97.7	98.3	0.960	<0.001
TP53	0.715	3354.304	62.8	54.1	0.169	<0.001
PON-1	0.939	7.1630	95.3	72.1	0.674	<0.001

The figure 5 illustrates the comparative diagnostic performance of the three biomarkers in identifying hypertensive smokers.8-OHdG demonstrated the highest diagnostic accuracy (AUC=0.999) followed by PON-1(AUC=0.939) while TP53 Showed significant predictive value(AUC=0.715). All markers reached statistical significance with $P < 0.001$, indicating their reliability in clinical assessment even under pharmacological management with Amlodipine.

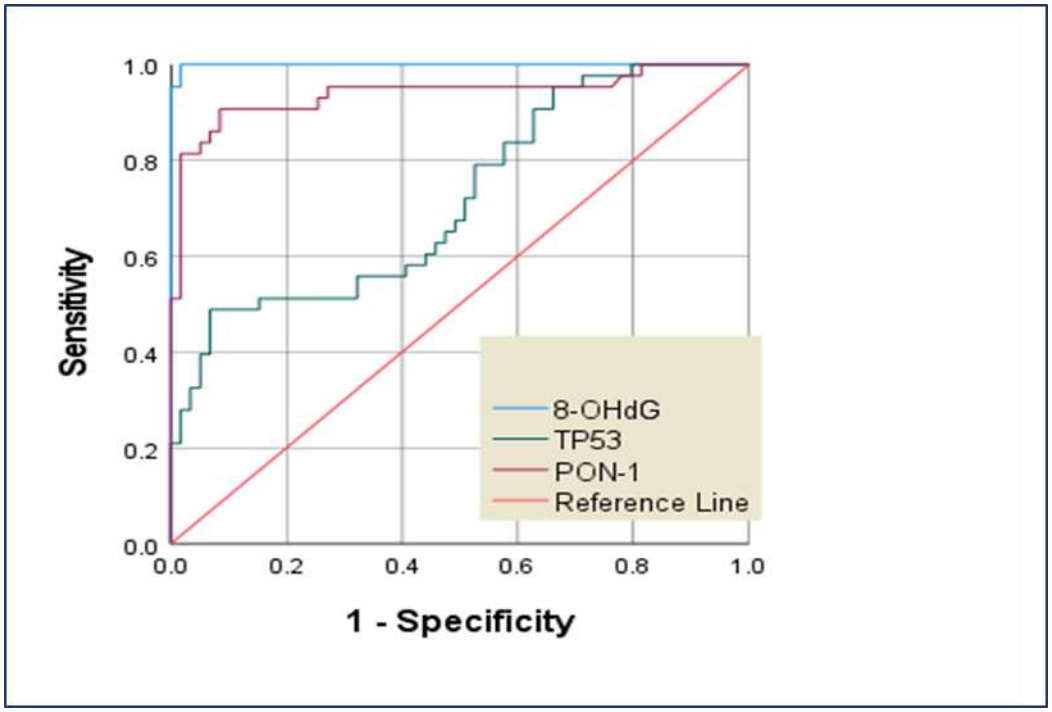


Figure 2:combined ROC curves for 8-OHdG ,PON-1,and TP53

The table 7 presents the risk assessment analysis ,focusing on the predictive value of serum 8-OHdG,PON-1,and TP53 in identifying the likelihood of developing hypertensive complications among chronic smokers. By calculating odd ratio (OR) and 95% confidence intervals(Cl),this analysis quantifies the relative risk associated with the depletion of antioxidant defenses and the escalation of DNA damage markers. This assessment is pivotal for understanding how physiological shifts- measured through these biomarkers serve as early warning signals for cardiovascular deterioration ,even in patients receiving antihypertensive therapy such as Amlodipine.

Table 7: Risk assessment for hypertension in smoker participants (adjusted for age, BMI, sex, and type of smoke).

Parameter	OR	95% CI	p-value
TP53	1.000	1.000-1.001	0.097
8-OHdG	2.559	0.991-6.606	0.052
PON1	0.375	0.256-0.550	<0.001

DISCUSSION:

The findings of the present study demonstrates that smoking significantly affects oxidative DNA damage, and blood pressure levels. No significant differences were observed in age or body mass index between the study groups ($p > 0.05$), indicating appropriate comparability. However, smoking behaviors differed markedly, with hypertensive smokers exhibiting higher consumption of cigarettes, waterpipe (narghile), and electronic vaping devices compared with normotensive smokers, suggesting that both intensity and mode of tobacco use contribute to hypertension risk, as supported by recent epidemiological evidence (9)

A clear physiological and biochemical distinction was observed between healthy controls and smokers, particularly among hypertensive individuals.The result show a interaction of smoking and hypertension that increase oxidative stress which is synergistic.And impairs antioxidant defense mechansims . This has been supported by substantially lowerd. Paraoxanase-1(PON-1) functioning and the presence of high level of oxidative DNA damage and genomic instability indicators,such as 8-hydroxy-2´-deoxyguanosine (8-OHdG) and tumor protein (TP53).Such finding are in line with the past reports.proving that tobacco smoke produces surplus reactive oxygen species (ROS), resulting in damage of DNA and inability to use antioxidant enzyme(5, 10).

Amlodipine was used to treat all hypertensive participants of this study. Although lipid inhibition has been reported to be an antioxidant effect of Amlodipine . Peroxidation , the current evidence indicates that they are not enough to neutralize the oxidative stress caused by smoking.(11).

The continual decrease in PON-1 activity , along with the increased levels of 8-OHdG IN The treated group, reveals that blood pressure control is not sufficient to prevent . smoking induced oxidative stress . This antioxidant gap can be attributed to direct . oxidative modification and inactivation of PON-1 by reactive constituents of tobacco smoke ,excessive production of ROS which surpasses endogenous antioxidant capacity (5, 12).

The significant rise in 8-OHdG levels of hypertenive smokers indicates high levels of oxidative DNA damage , which is expected given its proven status as a valid biomarker of oxidative stress(13). This genotoxic stress seems to induce tp53 upregulation as a compensatory response to induce DNA repair or apoptosis in accordance with known evidence of tabacco carcinogen-mediated cellular response through p53.(14). The elevated TP53 levels observed in this study therefore indicate a sustained state of genomic stress driven by ROS overproduction.

These results in aggregate imply a specific biochemical mechanism according to which smoking . Inhibits PON-1 action by oxidatively altering its actives sites , thus. Decrease antioxidant defenses and fostering vascular damage . this aligns with researches that emphasize the sensitivity of PON-1 to the enviroment and life style, including smoking(5, 6). The need for supplemental antioxidant method in hypertensive smokers is supported by the persistence of oxidative stress in spite of antihypertensive medication . Moreover, a TP53 mediated genomic response is maintained by the persistent oxidative imbalance, which is represented by high 8-OHdG levels. This suggests that amount of ROS produced by tabacco smoke . Surpasses the ability of endogenous repair systems.Amlodipine is useful for controlling hemodynamics, but it cannot completely restore redox equilibrium when smoke expossure persists . This emphasize how crucial quitting smoking is as the main treatment approch to lessen oxidative DNA damage and enhance vascular results.(15).

Moreover, comparative studies of the smoking modalities showed no significant differences in the 8-OHdG and TP53 levels between cigarette , water pipe (narghil),and electronic cigarette (vape), users indicating that all types of tobacco exposure cause similar oxidative and genotoxic effects. This conclusion is justified by the fact that both traditional tobacco smoke and electronic cigarette aerosols produce harmful oxidants and other toxic substances that are able to damage the DNA (16-19).Thus, the assumption that electronic cigarette is a safer option is not justified at the molecular level .

Finally, the combined receiver operating characteristic (ROC) analysis highlights that 8-OHdG (AUC = 0.999) and PON1 (AUC = 0.939) are more diagnostic sensitive than TP53 (AUC=0.751) in the detection of hypertension smokers . this confirms that oxidative DNA damage and antioxidant depletion markers are more valid indicators of vascular stress caused by smoking . the overlap of these biomarkers indicates a disruption of cellular defense mechanisms in a multidimensional manner , which supports the central role of oxidative stress in vascular pathology of smoking (9).

CONCLUSION:

The study confirms that smoking has a huge negative impact on the antioxidant defense damages genetic damage (PON-1,TP53). Notwithstanding the combined effect of hypertension and smoking , administration of Amlodipine , continued to induce apparent oxidative and genetic damage . The data indicate that there are only lowering blood pressure is insufficient to reduce the oxidative stress caused by smoking ,therefore, necessitating further antioxidant intervention along with anti-hypertensive treatment.

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