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Increased Serum Level of 8-Hydroxy-2'-Deoxyguanosine may be an Indication of Pesticides Induced DNA Damage among Indian Farmers

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ABSTRACT

The aim of the present hospital based study is to assess the serum levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) among 152 subjects. A total of 152 subjects, categorized into 3 groups: (i) pesticides exposed group (N=60), (ii) pesticide un-exposed group (N=42) and (iii) healthy controls group (N=50) were recruited for the study following the inclusion and exclusion criteria. The blood was drawn from the eligible subjects and Enzyme Immuno Assay (EIA) was performed to assess the 8-OHdG levels in serum. Appropriate statistical methods were used to analyse the study data. Assessment showed that pesticides exposed group has higher levels of serum 8-OHdG as compared to un-exposed group and healthy controls. Age and duration of exposure had an impact on the levels of serum 8-OHdG.The higher serum levels of 8-OHdG may be a marker for pesticides-induced oxidative DNA damage.

Keywords: pesticides; exposure; oxidative stress; 8-hydroxy-2'-deoxyguanosine (8-OHdG).

INTRODUCTION

Chemical control of pests is a common practice in agriculture. Though, pesticides are beneficial in mitigating the infestation of various pests and in improving the agricultural yield, they also have detrimental impacts on the health of human and environment (Kim et al. 2017). Widespread use of pesticides in modern farming practices worldwide lead to unintentional exposure among humans, especially among the occupationally exposed farmers. Repeated exposure to pesticides can also cause damage to DNA such as Sister Chromatid Exchange, double stranded breaks etc., leading to adverse health effects viz., neurodegenerative and reproductive disorders, and birth defects which not only result in altered disease susceptibility but also progression of cancers (Mostafalou and Abdollahi, 2013; Jablonska-Trypuc 2017; Sabarwal et al. 2018).

Oxidative stress due to exposure to environmental chemicals occurs to lipids of cell membranes as well in both nuclear and mitochondrial DNA. Pesticide induced oxidative stress was reported earlier for organophosphates, synthetic pyrethroids and carbamates using different genotoxic assays and 8-OHdG (Ogut et al. 2011; Zepeda Arce et al. 2017; Hazarika and Deka 2017;

Intranuovo et al. 2018). It is a known fact that the toxic mechanism of the chemical substances is by the formation of Reactive Oxygen Species (ROS) in the cell, because of their capability to interact with the most biologically significant target bases of the DNA, which cause imbalance between the free radicals and antioxidant defences in the lipids and thereby produce varieties of oxidation products leading not only to oxidative stress, but also the oxidative damage (Abdollahi et al. 2004; Dizdaroglu et al. 2002; Intayoung et al. 2020). Among all other bases, the guanosine is most susceptible to oxidative damage and produces8-OHdG, an adduct, which can give rise to C:G to A:T transversion mutations. Therefore, the formation of 8-OHdG is considered as a sensitive biomarker for not only assessing the oxidative stress but also the cytogenetic damage induced due to chronic exposure to organophosphorus pesticides (Valavanidis et al. 2009; Mishra et al. 2015, Oh et al. 2016; Markkanen 2017; Jelic et al. 2018; Eldin et al. 2019).

There are several reports which demonstrated the increased DNA damage and elevated oxidative stress levels among farmers who were exposed to pesticides, when compared with non-farmers(Da Silva et al. 2012; Wafa et al. 2013; Taghavian 2016). The aim of the present investigation was to assess the levels of 8-OHdG among the farmers, occupationally exposed to pesticides and compare with non - farmers who do not use pesticides and visiting the MNJ Institute and subsequently to compare them with the healthy controls in order to assess the pesticide induced oxidative stress.

METHODOLOGY

This is a hospital based case-control study. The study subjects recruited were those visiting the MNJ Institute of Oncology & Regional Cancer Centre. The study was approved by the ethics committee of National Institute of Nutrition, Hyderabad, T.S., India (NIN Protocol Number-CR/08/II/2019) and MNJ Regional Cancer Centre, Hyderabad, T.S., India (Reg. no.: ECR/227/Inst/AP/2013/RR-16). A written informed consent was obtained from all the subjects before collecting the samples.

The inclusion criteria were:

i. Subjects with history of exposure to pesticides (N=60).
ii. Subjects who neither have history of exposure to pesticides nor involved in farming activities (N=42).
iii. Healthy controls who neither had any history of exposure to pesticides nor were involved in farming activities (N=50).

Subjects less than 18 years of age and diagnosed with chronic disorders such as hypertension, diabetes, AIDS and kidney disorders were excluded from the study.

The information pertaining to the demographic particulars such as age, gender, income group, dietary habits, occupational status, illness, their personal habits like smoking and consumption of alcohol were collected from all the three groups of subjects. In case of exposed group, types of crops cultivated, types of pesticides used if any, earlier, number of years of exposure in farming activities, mode of usage, knowledge on pesticide usage, any previous morbidities due to pesticide poisoning (intentional/accidental), usage of personal protective equipment, (PPEs, like gloves, masks and apron), knowledge on toxicity symbols, reading of pesticide label information, storage of pesticides, precautionary measures taken after spraying pesticides were also collected using a pre-tested questionnaire.

Two millilitre of blood collected by venepuncture using vacutainer tubes was centrifuged to separate the serum and was stored at -80^{o}C till analysed. 8-OHdG was analysed using commercial ELISA kits (Elabscience, USA). Briefly, 50µl of standard and 50µL of serum samples were added in respective wells of a 96 well plate. Biotinylated detection Ab (1:100 dilutions) working solution was added to the wells, followed by incubation for 45 minutes at 37^{o}C. After incubation, the plates were

washed and aspirated thrice with washing buffer to which 100µl of HRP-streptavidin conjugate solution was added and were incubated again for 30 minutes at 37^{o}C.Subsequently, the plates were aspirated and washed again using washing buffer followed by addition of 90µL substrate reagent and incubated at 37^{o}C for 15 minutes. The incubated wells were added with 50µL of stop solution and the absorbance was read at 450nm using a micro plate reader (BioTek Instruments).

Data Analysis

The data was analysed using the IBM SPSS 19.0. The descriptive variables were represented as mean (standard deviation), frequency and percentages. One way ANOVA was used to analyse the significant difference between the groups followed by an independent t-test to compare the statistical significance between serum 8-OHdG levels among the three groups of subjects. Correlation and regression analysis was used to determine the relationship between age, exposure, personal habits and serum 8-OHdG levels among all the three groups of subjects. Statistical analysis was conducted at 5% level of significance.

RESULTS

Table 1: Demographic characteristics of subjects (n=152)

		Group							
		Exposed		Unexposed		Healthy Control		Total	
		N	%	N	%	N	%	N	%
Sex	Male	38	63.3	25	59.5	29	58.0	92	60.5
	Female	22	36.7	17	40.5	21	42.0	60	39.5
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Educational Status	Illiterate	18	30.0	10	23.8	-	-	28	18.4
	Literate	42	70	32	23.8	50	100.0	124	81.6
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Major Occupation	Agriculture	60	100.0	-	-	-	-	60	39.5
	Other than agriculture	-	-	42	100.0	50	100.0	92	60.5
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Family engaged in agriculture	Yes	37	61.7	0	0	0	0	37	61.7
	No	23	38.3	0	0	0	0	23	38.3
	Total	60	100.0	0	0	0	0	60	100.0
Dietary Habits	Vegetarian	0	0.0	0	0	1	2.0	1	0.7
	Non-vegetarian	60	100.0	42	100.0	49	98.0	151	99.3
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Beedi (Indian Cigar)	Yes	7	11.7	1	2.4	4	8.0	12	7.9
	No	53	88.3	41	97.6	46	92.0	140	92.1
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Cigarettes	Yes	6	10.0	3	7.1	6	12.0	15	9.9
	No	54	90.0	39	92.9	44	88.0	137	90.1
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Cigar	Yes	5	8.3	2	4.8	3	6.0	10	6.6
	No	55	91.7	40	95.2	47	94.0	142	93.4
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Tobacco	Yes	10	16.7	6	14.3	5	10.0	21	13.8
	No	50	83.3	36	85.7	45	90.0	131	86.2
	Total	60	100.0	42	100.0	50	100.0	152	100.0
Alcohol	Yes	10	16.7	5	11.9	8	16.0	23	15.1
	No	50	83.3	37	88.1	42	84.0	129	84.9
	Total	60	100.0	42	100.0	50	100.0	152	100.0

Table 2: Serum 8-OHdG levels (ng/mL) among exposed, un-exposed and healthy controls (N=152)

Exposed		Un exposed		Healthy Controls		
N	8-OHdG Mean ± SD	N	8-OHdG Mean ± SD	N	8-OHdG Mean ± SD	p < 0.001
60	32.435±11.30	42	23.579± 8.06	50	18.34 ±5.14	

The mean age of exposed, unexposed and controls were found to be 38.9, 33.4 and 24.3 years respectively. The other demographic particulars and personal habits of the subjects were shown in Table 1. The self-reported information on the

particulars of pesticide spraying activities among the subjects was also presented in Fig. 1. It was found that Acephate, Chlorpyrifos, Cyalothrin, Dichlorovos, Fenitrothion, Monocrotophos, Phorate, Phosmet, Profenofos, Quinalphos were the major pesticides used by the farmers residing in Andhra Pradesh and Telangana states of India. The serum 8-OHdG levels analysed in all the three groups of subjects and this found to have shown a significant difference ($p<0.001$) among the exposed subjects than the unexposed group and the healthy controls (Table 2).

Table 3: Serum 8-OHdG levels among exposed (N=60) in relation to the duration of exposure to pesticides

Duration of exposure (years)	Exposed (N)	Avg. no. of hours of exposure/day (hr/day)	Avg. no. Of Months of exposure/yr (Mean±SD)	Serum 8-OHdG levels Mean±SD (ng/mL)
<7	21	1.8±1.5	1.5±0.7	30.7±10.7
8-15	20	1.7±1.7	1.4±0.7	32.0±10.1
16 & above	19	2.7±2.0	1.5±0.6	34.6±13.1

Table 4: Spearman's rank Correlations

		Age	Sex	Group	Duration of exposure (years)	Tobacco	Alcohol	8OHdG
Age	r	1.000	0.119	-0.549**	0.505**	-0.285**	0.043	0.310**
	P-value		0.144	<0.001	<0.001	<0.001	0.599	<0.001
	N	152	152	152	60	152	152	152
Sex (male, female)	r	0.119	1.000	0.047	-0.079	0.089	0.228**	0.032
	P-value	0.144		0.565	0.547	0.274	0.005	0.698
	N	152	152	152	60	152	152	152
Group (farmer, non-farmer, control)	r	-0.549**	0.047	1.000		0.081	0.012	-0.626**
	P-value	<0.001	0.565			0.321	0.883	<0.001
	N	152	152	152	60	152	152	152
Duration (years)	r	0.505**	-0.079	-	1.000	-0.118	0.014	-0.072
	P-value	0.000	0.547	-		0.368	0.914	0.582
	N	60	60	60	60	60	60	60
Tobacco use	r	-0.285**	0.089	0.081	-0.118	1.000	0.203*	-0.075
	P-value	<0.001	0.274	0.321	.368		0.012	0.362
	N	152	152	152	60	152	152	152
Alcohol use	r	0.043	0.228**	0.012	0.014	0.203*	1.000	-0.013
	P-value	0.599	0.005	0.883	0.914	0.012		0.874
	N	152	152	152	60	152	152	152
8-OHdG level	r	0.310**	0.032	-0.626**	-0.072	-0.075	-0.013	1.000
	P-value	<0.001	0.698	<0.001	0.582	0.362	0.874	
	N	152	152	152	60	152	152	152
***. Correlation is significant at the 0.01 level (2-tailed).*								
**. Correlation is significant at the 0.05 level (2-tailed).*								

Table 5: Multiple linear regression analysis

	Unstandardized Coefficients		t	P-value	95.0% Confidence Interval for B	
	B	Std. Error			Lower Bound	Upper Bound
(Constant)	43.14	8.34	5.17	<0.001	26.66	59.63
Sex (male, female)	1.74	1.53	1.14	0.255	-1.27	4.76
Age	-0.05	0.08	-0.61	0.546	-0.20	0.11
Group (farmer, non-farmer, control)	-9.21	1.83	-5.02	<0.001	-12.84	-5.59
Alcohol use	0.39	2.11	0.19	0.852	-3.77	4.55
Tobacco use	0.42	2.28	0.18	0.856	-4.09	4.92
Current Illness	-3.51	3.23	-1.09	0.278	-9.89	2.87

The 8-OHdG levels among all the three groups of subjects found to have shown an increase by age, however, a slight decrease in the levels among the subjects having more than 35 years of age was also noticed (Fig.2). A positive correlation was observed between duration of exposure and 8-OHdG levels among the farmers having less than 7 years of exposure and a decrease in levels among the farmers with 8 and above years of exposure (Table 3 and Fig.3). The linear regression analysis showed a positive correlation between age and serum 8-OHdG levels among the farmers below 35 years of age. There was a constant increase in 8-OHdG levels in the farmers with age up to 35 years of age and decline was observed in the same above 35

years (Fig.4). It was also found that for every one year increase in the age, there is an increase in the 8-OHdG levels by 0.24ng/mL (Fig. 2) in the farmers, while, the variation in serum 8-OHdG levels explained by age as a factor was only 7% (R^2=0.069). However, no significant association was observed with respect to the serum 8-OHdG levels and personal habits of smoking and alcohol consumption among the exposed group (Table 1).

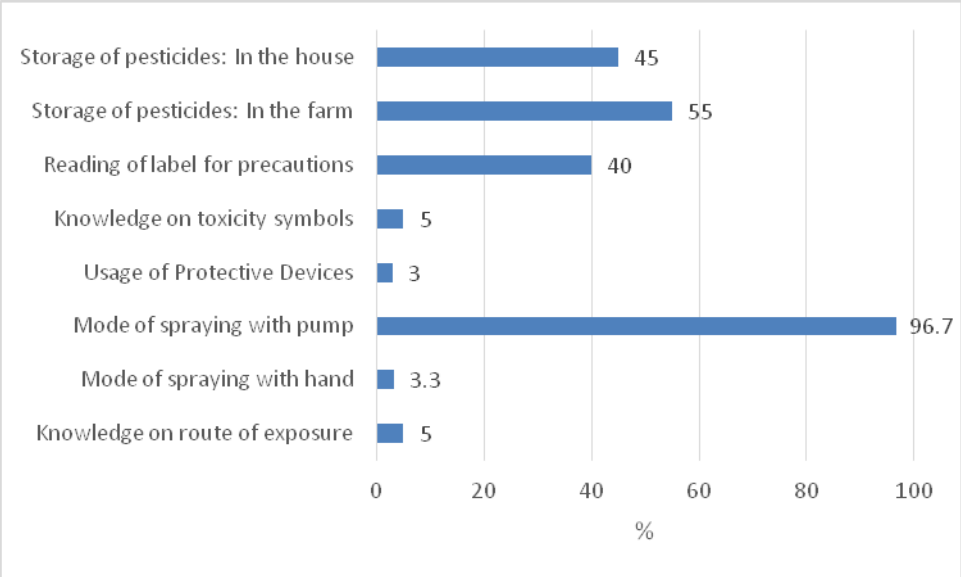

Fig.1: Knowledge, attitude and practices on the use of pesticides (N=60)

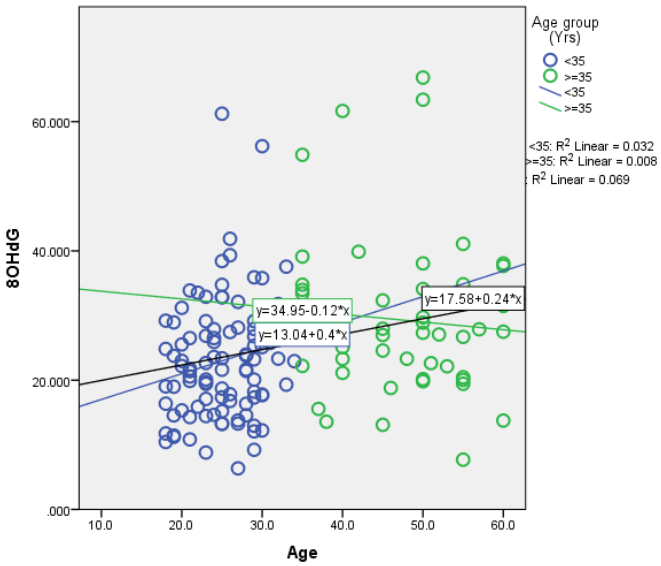

Fig. 2: Linear regression between age and 8-OHdG levels among all the groups

The Spearman's rank correlation analysis suggests that the 8-OHdG was positively correlated with the age and the elevation was found to be more in the exposed group as compared to the un-exposed group and healthy controls. The multiple linear regression analysis though showed that the age is explaining about 7% of the variation in the 8-OHdG among all the three groups of subjects but the exposed group (farmers) has significantly higher levels of 8-OHdG as compared to both the groups. It was further observed that, the Knowledge, Attitude and Practice followed by the exposed group shown no significant association in the elevation of 8-OHdG

levels, but, as the duration of exposure increased, an increase in the elevation of 8-OHdG levels was observed, thereby increasing the 8-OHdG levels among the exposed group. However, no significant association reported between the 8-OHdG levels and the personal habits among all the three groups was observed (Tables 4 and 5).

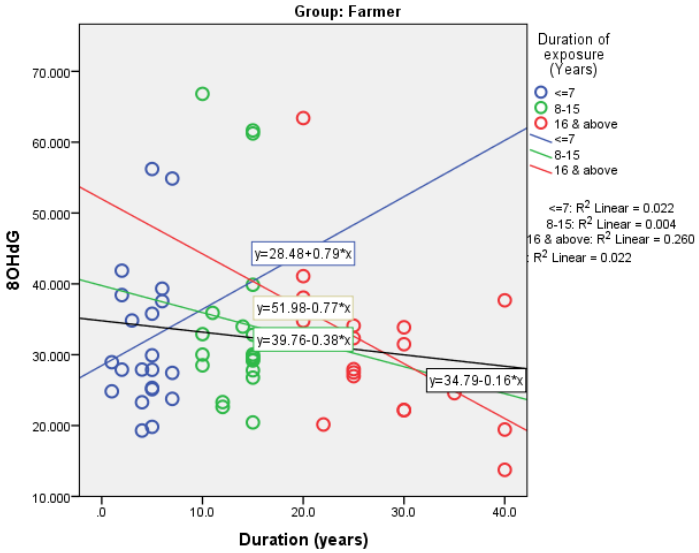

Fig 3: Linear regression between duration of exposure and 8-OHdG levels among exposed group

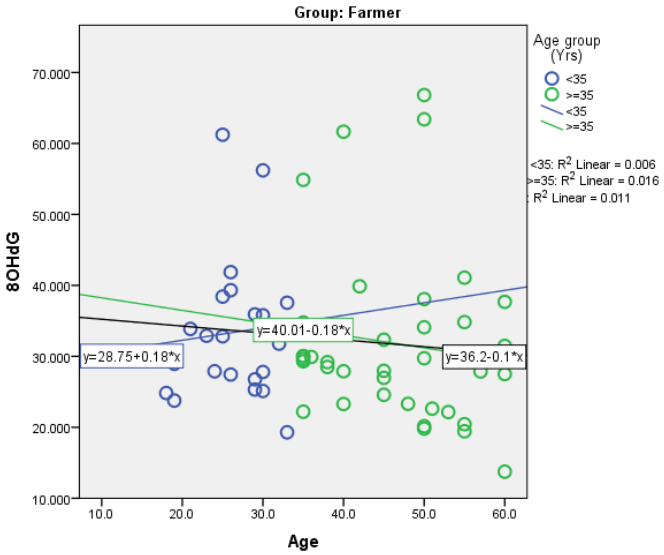

Fig 4: Linear regression between age and 8-OHdG levels among exposed group

DISCUSSION

Studies conducted earlier on the presence of urinary metabolites among the subjects exposed to pesticides may not exactly provide the information on the actual impact on health. However, lipid peroxidation and free radical induced damage such as 8-OHdG and their subsequent lead to chronic disorders are considered to be the potential biomarkers of pesticide exposure (Lee et al. 2017).

In the present study, it was observed that the exposure to pesticides might play a role in increasing the serum 8-OHdG levels. Study conducted elsewhere showed elevated levels of 8-OHdG among the apple farmers in Thessaly Region, Greece (Koureas et al. 2014). Similarly, in another study, usage of atrazine was found to have been associated

with increased levels of 8-OHdG among corn farmers in Iowa, United States of America (Lerro et al. 2017). In the present investigation, among the 60 exposed, only three had knowledge on the route of exposure and on the toxicity symbols reflected on pesticide containers, while 70% of them were identified as illiterates and hence, the reason, for not reading the label information.

It was interesting to note that there is no significant difference between the 8-OHdG levels and their personal habits such as smoking and alcohol consumption, among all the three groups of study subjects. Similar observations were made earlier among pesticide sprayers (Mishra et al. 2015). On contrary, another study conducted elsewhere reported elevated levels of 8-OHdG and strong association with smoking (Kulikowska-Karpińska and Czerw 2015; El-Khawanky et al. 2018). It was further evident from the present findings that the subjects exposed to pesticides for less than 7 years showed the minimum mean values of serum 8-OHdG as compared to those exposed for more than 16 years. In a study conducted previously, it was found that increased exposure to organophosphorus pesticides was associated with higher levels of urinary 8-OHdG and total Di Alkyl Phosphates (Ding et al. 2012). Similarly, prolonged exposure to organophosphate pesticides among pesticide sprayers showed increased levels of 8-OHdG(Lee et al. 2017). In a study conducted among Bolivian famers, it was found that high level of exposure to some pesticides was associated with increased risk of genotoxic damage (Cuenca et al. 2019). Data are also available on the increased risk of elevated 8-OHdG among farmers who were exposed to different classes of pesticides, suggesting that pesticides might play a crucial role in inducing oxidative stress (Jacobsen-Pereira et al. 2018).

In the present investigation, though there found a positive correlation between an elevation in the 8-OHdG among all the groups of the subjects with respect to the age, it was more among the exposed than the unexposed and healthy controls indicating that exposure to pesticides might have led to increase in the oxidative DNA damage. Similar observation was reported in other studies also (Taghavian et al. 2016; Wu et al. 2017; Korkmaz et al. 2018).

It was observed that with the progression in age, there was a simultaneous increase in the 8-OHdG levels by 0.24 ng/mL among the exposed group suggesting that age might be partially playing a pivotal role in the elevation of 8-OHdG only till younger age groups of adults (35 years of age). In contrast, a study conducted among 67 farmers who were exposed to organophosphorus pesticides and 67 control group, substantial gains though were observed in the oxidative DNA damage among the farmers, but no significant correlations could be made between age and 8-OHdG levels (Taghavian et al. 2016).

No definite conclusions can be drawn from the results of the present investigation, as the elevation in the levels of 8-OHdG observed was only among pesticide exposed group of below 35 years of age group as compared to unexposed group and subsequently it was found to be similar among all the three groups. Similarly, the elevation observed with respect to the duration of exposure was found significant among farmers exposed for 7 years only and subsequently there is no significant elevation among exposed for more than 7 years and above, suggesting that exposure did not play a crucial role after certain period of occupational exposure. However, the smaller sample size may be considered as a limitation in drawing any definite conclusion in the present study. Hence, future studies using a larger sample size on detailed analysis of pesticide residues and their metabolites in the body fluids of subjects (with or without known history of exposure to pesticides) in combination with the estimation of 8-OHdG levels and genetic polymorphism if any, may provide better insights on the

association of 8-OHdG levels and pesticide exposure.

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Ethical Approval: Approved

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