

Biological Monitoring of Polycyclic Aromatic Hydrocarbons as a Possible Risk Factor of Hepatocellular Carcinoma Among Cases of Chronic Active Hepatitis B and C

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Abstract: Background: Polycyclic aromatic hydrocarbons (PAHs) are among the most carcinogenic, mutagenic and toxic contaminants. Their exposure and metabolism to DNA-reactive metabolites in the body are considered to contribute to the aetiology of many types of the human cancers. **Objectives:** to find out if exposure to polycyclic aromatic hydrocarbons is a risk factor for development of hepatocellular carcinoma among the exposed cases, to detect if the smoking is an augmented factor for development of hepatocellular carcinoma among exposed cases, and to find the effect of sociodemographic characteristics of cases of hepatocellular carcinoma exposed to hydrocarbons. **Subjects and Methods:** A case control study was conducted between the period from the first of March 2015 to end of August 2017. The study was conducted in the outpatient clinic of the Department of Hepatology and Gastroenterology at Theodor Bilharz Research Institute (TBRI). The minimum sample size required for the present study was calculated using Epi info program, considering following data: Two sided Confidence level = 95%, Power of test = 80%, Ratio of control: cases = 1:1, Percent of control exposed = 21%, Percent of cases exposed = 42 % and Odds ratio = 2.8. Kelsey estimated number of cases = 77 and number of control = 77 subjects. All subjects of both groups were interviewed. Every patient was subjected to the selected interview sheet and biological monitoring of urinary 1-hydroxy pyrene as a biomarker for PAHs exposure. **Results:** 73% of cases of HCC had increased level of 1-hydroxy pyrene in urine with statistical significance difference when compared to controls. There was significant positive association between exposure to PAHs and development of HCC among case group (OR = 4.9). There was significant association between smoking and abnormal high level of 1-hydroxy pyrene in urine (OR = 1.7), among the case group. There was significant positive association between exposure to PAHs and development of HCC among males (OR = 1.6). There was neither statistical significance difference nor positive association between exposure to PAHs and development of HCC in urban areas (OR=0.8). There was statistical significance positive association between exposure to PAHs and development of HCC among smoker (OR=1.7). There was neither statistical significance nor positive association between exposure to PAHs and development of HCC among patients with chronic active hepatitis C (OR=0.6). There was a highly positive correlation between 1-hydroxy pyrene and Alfa Feto Protein (AFP) among positive cases of 1-hydroxy pyrene in case group (OR=316.25). **Recommendation:** Prevention programs aimed to elimination of exposure to PAHs is needed. Environmental monitoring of PAHs in different residential areas in different governorates for detection of source of pollution with PAHs in air, soil and water is needed.

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1. Introduction:

Polycyclic aromatic hydrocarbons (PAH) are major pollutants in the environment formed during incomplete combustion of organic materials such as gasoline, diesel fuel, coal and oil. The substances are therefore found in heavily polluted air, water, soil and smoked food (WHO, 2013).

Polycyclic aromatic hydrocarbons (PAHs) are among the most carcinogenic, mutagenic and toxic contaminants. Their exposure and metabolism to DNA-reactive metabolites in the body are considered

to contribute to the aetiology of many types of the human cancers (EEAA, 2011).

Uptake of PAH in the body may be monitored by different biomarkers, for example metabolites in urine, urinary thioethers, urinary mutagenicity, PAH– protein adducts and PAH–DNA adducts (Angerer and Schaller 2009).

Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide, Its incidence is increasing, ranging between 3% and 9% annually depending on the geographical location, and

variability in the incidence rates correspond closely to the prevalence and pattern of the primary etiologic factors (El-Zayadi et al., 2011).

Ezzat et al., 2014 stated that during the last 5-10 years, high incidence of HCC in Egypt, which reach about 21% in cirrhotic patients.

In a single center study over a decade in Egypt reported that, chronic infections with HBV or HCV have both been recognized as human liver carcinogens with a combined attributable fraction of at least 75% of all HCC cases (Hassan et al., 2011).

In Egypt, extensive research over the past decade has documented high and increasing HCC incidence resulting from chronic HBV and HCV infections (Nadia et al., 2007).

It was observed that the incidence of HCC all over the world is increasing year by year with no definite exploration for this problem. However, PAHs might be a risk factor especially among the cases of chronic active hepatitis B and C. The ultimate objective of the present study is to reduce the development of HCC among the cases of chronic active hepatitis B and C exposed to polycyclic aromatic hydrocarbons.

Objectives:

To find out if exposure to polycyclic aromatic hydrocarbons is a risk factor for development of hepatocellular carcinoma among the exposed cases, to detect if the smoking is an augmented factor for development of hepatocellular carcinoma among exposed cases, and to find the sociodemographic characteristics of cases of hepatocellular carcinoma.

2. Subjects and Methods:

Type of the study: A case control study was conducted between the period from the first of March 2015 to end of August 2017. Place of the study: The study was conducted in the outpatient clinic of the Department of Hepatology and Gastro-entriology at Theodor Bilharz Research Institute (TBRI). Sample size estimation: The minimum sample size required for the present study was calculated using Epi info program, considering following data: Two sided Confidence level = 95%, Power of test = 80%, Ratio of control: cases = 1:1, Percent of control exposed = 21% (El-Zayadi et al., 2011), Percent of cases exposed = 42 % and Odds ratio = 2.8. Kelsey estimated number of cases = 77 and number of control = 77 subjects. The sampling technique: Cases were selected from all cases registered at the place of the study and regularly follow up at the outpatient clinic. Cases was defined as patients with chronic active hepatitis B, C or both with hepatocellular carcinoma (HCC). They were numbered and total was 120 patients. By using simple random technique, the cases were selected using table of random number to reach

77 cases. Controls were selected from all cases registered at the place of the study and regularly follow up at the outpatient clinic. Controls was defined as patients with chronic active hepatitis B, C or both without hepatocellular carcinoma (HCC). They were numbered and total was 400 patients. By using simple random technique, the controls were selected using table of random number to reach 77 controls. Research Tools: An interview sheet: all the following data were collected from all subjects in the examined groups: Personal history: including the name of patient, age, sex, residence, marital state and special habits of medical importance (smoking). Occupational history: including the nature of the job, the duration of exposure, worked hours per week and the past occupations. Medical history: of chronic active hepatitis B and/or C and HCC (which documented by recent ultrasonography and/or Triphasic CT). Clinical examination: general and local examination. Investigations: as liver function tests, ultrasonography, triphasic CT, alpha feto protein and liver biopsy or fibro scan. Biological monitoring of 1-Hydroxy pyrene in urine: as a biomarker of exposure to polycyclic aromatic hydrocarbons. Phases of the study: A- Preparatory phase: The preparatory phase took about six months from the first of March 2015 till the end of August 2015. During this phase the following steps were conducted. Survey of literature: A review of literature was conducted in order to explain the risk of occupational and environmental exposure to polycyclic aromatic hydrocarbons and biological monitoring of them. A survey of literature was obtained from: The periodic medical journals especially recently published ones, some trusted web sites, OSHA reports and documents, some text books and some previous researches (national and international). Ethical Administrative consideration: Written Permission to implement the study was obtained from Ethic Committee of both Al-Azhar Faculty of Medicine and TBRI. Written permission to implement the study was obtained from TBRI hospitals authority from the general manager of TBRI and Head of the department of hepatology and Gastroentriology at TBRI. Oral approval was taken from every subject before subjecting him to the interview sheet, urine sampling and clinical examination. Pilot study: Pilot study was conducted to assess patient's impression, reaction and cooperation with the study. The pilot study included (16) patients (8 subjects of case group and 8 subjects of control group). No modification of the interview sheet was conducted after the pilot study as respecting culture and time of the examined patients, so the pilot sample was included in this study. B- Implementation phase: The implementation phase took about one year, from the first of September 2015 till the end of August

2016. During this phase the researcher interviewed all included patients separately. Every patient was subjected to the selected interview sheet and biological monitoring of urinary 1-hydroxy pyrene as a biomarker for PAHs exposure. It took about one and half hour for each subject. C- Evaluation phase: The evaluation phase took about one year from the first of September 2016 till the end of August 2017. During this phase the collected data were organized, tabulated and analyzed by S.P.S.S program version 17. Then Discussion, conclusion, recommendation and summary were addressed.

3. Results:

Table (1) shows the level of 1-hydroxy pyrene in urine among the studied groups. There was statistical significance difference between exposed and non-exposed groups $p < 0.001$ (73% of cases showed abnormal level and about 50% of them showed moderate elevation). It was shown that there was a positive association between exposure to PAHs and development of HCC (OR = 1.4).

Table (2) shows the distribution of sex among the positive cases of 1-hydroxy pyrene in urine among the studied groups. There was not statistical significance difference between the two groups $p > 0.05$ but it was noticed that males had 1.65 fold more than females to develop HCC on top of chronic active hepatitis B and C when exposed to PAHs (OR = 1.65).

Table (3) shows the distribution of residence among the positive cases of 1-hydroxy pyrene in urine among the studied groups. There was not statistical significance difference between the two groups $p > 0.05$ and it was observed that there was not an association

between exposure to PAHs in urban areas and development of HCC on top of chronic active hepatitis B and C in case group (OR =0.8).

Table (4): shows the Distribution of smoking habit among the positive cases of 1-hydroxy pyrene in urine among the studied groups. In spite of there was no statistical significance difference between the two groups, it was found that there was a positive association between smoking and development of HCC on top of chronic active hepatitis B and C in case group when exposed to PAHs (OR = 1.7).

Table (5): This table shows the types of hepatitis among the positive cases of 1-hydroxy pyrene in urine among the studied groups. It was noted that there was no statistical significance difference between the two groups $p > 0.05$. Also, it was noticed that there was not an association between cases of chronic active hepatitis C and development of HCC when exposed to PAHs (OR = 0.6).

Table (6): shows that there was a very high association between the presence of 1-Hydroxy pyrene in urine and elevated AFP (Alfa Feto protein) among the cases with positive 1-hydroxypyrene in urine (RR = 316.25). Also, it was found that there was a statistical significance difference between the exposed and non- exposed group $p < 0.001$.

Table (7): shows that the relation between positive 1-Hydroxy pyrene in urine and signs of decompensation among the studied groups. It was found that there was statistical significance difference between the two groups $p < 0.05$ but it was noticed that there was a negative association between 1-hydroxy pyrene and signs of decompensation.

Table (1): 1-Hydroxy pyrene in urine as a biomarker of exposure to Polycyclic Aromatic Hydrocarbons (PAHs) among the studied groups

	Case group N = 77		Control group N = 77		Chi-square		Odds ratio (OR)
	No.	%	No.	%	X ²	P-value	
*1-hydroxy pyrene in urine:							
Normal level	21	27%	50	65%	21.9	0.0*	4.9
Abnormal level	56	73%	27	35%			
Total	77	100%	77	100%			
	Case group n = 56		Control group n = 27		Chi-square		
	No.	%	No.	%	X ²	P-value	
Types of abnormalities:							
High elevation	14	25%	0	0%	28.475	<0.001*	
Moderate elevation	28	50%	9	33.3%			
Low elevation	14	25%	9	33.3%			
Very low elevation	0	0%	9	33.3%			
Total	56	100%	27	100%			

Table (2): Distribution of sex among the positive cases of 1-hydroxy pyrene in urine among the studied groups

Sex	Positive 1-Hydroxy pyrene in urine				Chi-square		Odds Ratio (OR)
	Case group N = 56		Control group N = 27		X ²	P-value	
	No.	%	No.	%			
Male	39	69.6%	16	60%	0.8	0.3	1.6
Female	17	30.4%	11	40%			
Total	56	100%	27	100%			

Table (3): Distribution of residence among the positive cases of 1-hydroxy pyrene in urine among the studied groups

Residence	Positive 1-Hydroxy pyrene in urine				Chi-square		Odds Ratio (OR)
	Case group N = 56		Control group N = 27		X ²	P-value	
	No.	%	No.	%			
Rural	21	37.5%	9	33.3%	0.1	0.7	0.8
Urban	35	62.5%	18	66.7%			
Total	56	100%	27	100%			

Table (4): Distribution of smoking habit among the positive cases of 1-hydroxy pyrene in urine among the studied groups

Smoking	Positive 1-Hydroxy pyrene in urine				Chi-square		Odds Ratio (OR)
	Case group N = 56		Control group N = 27		X ²	P-value	
	No.	%	No.	%			
Smoker	28	50%	10	37%	1.2	0.3	1.7
Non smoker	28	50%	17	63%			
Total	56	100%	27	100%			

Table (5): Types of hepatitis among the positive cases of 1-hydroxy pyrene in urine among the studied groups

Types of hepatitis	Positive 1-Hydroxy pyrene in urine				Chi-square		Odds Ratio (OR)
	Case group N = 56		Control group N = 27		X ²	P-value	
	No.	%	No.	%			
Hepatitis B	21	37.5%	7	26%	0.1	0.3	0.6
Hepatitis C	35	62.5%	20	74%			
Total	56	100%	27	100%			

N.B. There were no positive cases of 1-hydroxy pyrene in urine among the studied groups of both B and C.

Table (6): AFP among the positive cases of 1-hydroxy pyrene in urine among the studied groups

AFP	Positive 1-Hydroxy pyrene in urine				Chi-square		Odds Ratio (OR)
	Case group N = 56		Control group N = 27		X ²	P-value	
	No.	%	No.	%			
Normal	1	1.7%	23	85%	61.6	0.000*	316.25
Elevated	55	98.3%	4	15%			
Total	56	100%	27	100%			

Table (7): Signs of decompensation among the positive cases of 1-hydroxy pyrene in urine among the studied groups

Signs of decompensation	Positive 1-Hydroxy pyrene in urine				Chi-square		Odds Ratio (OR)
	Case group N = 56		Control group N = 27		X ²	P-value	
	No.	%	No.	%			
Present	35	62.5%	25	95%	8.2	0.004*	0.1
Absent	21	37.5%	2	5%			
Total	56	100%	27	100%			

4. Discussion:

Regarding biological monitoring of 1-Hydroxy pyrene in urine as a biomarker of exposure to Polycyclic Aromatic Hydrocarbons (PAHs) among the studied groups (Table 1), there was significant association between exposure to PAHs and development of HCC (OR = 4.9). This agrees with Lee et al., 2009; Shahataheri, 2009; Van Larebeke et al., 2010 and Hansen et al., 2013. Who reported the exposure to PAHs might be a risk factor of lung, kidney, renal and testicular cancer. Also, agrees with Jing Yang et al., 2017, who concluded that the data of their study reinforce that urinary 1-hydroxy pyrene can be a useful biomarker for evaluating total PAHs exposure and in assessing the effect of PAHs exposure on oxidative damage. This agrees with Guohang et al., 2012, who concluded that PAHs are found in the human rectal tissues or hepatic tissues. The content of PAHs in the human rectal tissues may have affection on the occurrence of rectal cancer while the content of PAHs in the hepatic tissues may have ones.

Concerning the relation of 1-Hydroxy pyrene in urine and the sex of examined groups (Table 2), there was significant statistical association between the presence of 1-Hydroxy pyrene in urine and sex of examined subjects and males had 1.65 fold more than females to develop HCC on top of chronic active hepatitis B and C when exposed to PAHs (OR = 1.6). This agrees with Dong and Lee, 2009, who reported that positive association between male and exposure to PAHs for development of cancer. But this disagrees with Yang et al., 2004, Chen et al., 2007 and Oanh et al., 2009, who found no association between sex and exposure to PAHs for development of cancer.

In the view of the relation of 1-Hydroxy pyrene in urine and the residence of the examined groups (Table 3), It was found that there was not statistical significance difference between the two groups, and no association between exposure to PAHs in urban areas and development of HCC on top of chronic active hepatitis B and C in the case group (OR = 0.8). This disagrees with Dong and Lee, 2009, who stated that increase the risk of cancer due to exposure to PAHs in the urban areas and explained that by more

exposure to industrial and mobile sources. However Yang et al., 2004, Chen et al., 2007 and Oanh et al., 2009 stated that increased exposure to PAHs in the rural areas might be due to primitive methods of cooking and heating.

As regards the relation of 1-Hydroxy pyrene in urine and smoking habit among the examined groups (Table 4). In spite of there was no statistical significance difference between the two groups, there was positive association between smoking and development of HCC on top of chronic active hepatitis B and C in the case group when exposed to PAHs (OR = 1.7), this agrees with Yang et al., 2009; Li and Ro, 2010; Poppi and Silva, 2015, who reported that positive association between smoking and development of HCC among cases of chronic active hepatitis B or C. This agrees also with Jing Yang et al., 2017, who found that smoking can significantly increase the level of 1-hydroxy pyrene in urine in cases exposed to PAHs and smoking will cause more serious DNA oxidative damage among the exposed cases to PAHs and agrees with Lannero E et al., 2008, who concluded that the major route of exposure to PAHs in the general population is from breathing ambient air polluted with PAHs and indoor eating food containing PAHs, cigarettes smoking or breathing smoke from open fire.

Regarding the relation of 1-Hydroxy pyrene in urine and different types of hepatitis among the examined groups (Table 5), there was neither statistical significance difference between the two groups nor association between cases of chronic active hepatitis C and development of HCC when exposed to PAHs (OR = 0.6). This might be explained by effect of hydrocarbons in development of hepatic cancer not determined with type of viral hepatitis.

As regards the relation of 1-Hydroxy pyrene in urine and AFP among the examined groups (Table 6), there was a highly positive association between abnormal level of 1-Hydroxy pyrene in urine and elevated AFP (OR = 316.25) and there was a statistical significance difference between exposed and non-exposed groups. This could be attributed to exposure to PAHs has a positive effect on the level of AFP.

Concerning the relation of 1-Hydroxy pyrene in urine and signs of decompensation among the examined groups (Table 7), there was negative association between the two abnormalities. This might be explained with abnormal liver functions depend on liver state of cirrhosis and cancer not the exposure to PAHs.

Conclusion:

73% of cases of HCC had increased level of 1-hydroxy pyrene in urine with statistical significance difference when compared to controls. There was significant positive association between exposure to PAHs and development of HCC among case group (OR = 4.9). There was significant association between smoking and abnormal high level of 1-hydroxy pyrene in urine (OR = 1.7), among the case group. There was significant positive association between exposure to PAHs and development of HCC among males (OR = 1.6). There was neither statistical significance difference nor positive association between exposure to PAHs and development of HCC in urban areas (OR=0.8). There was statistical significance positive association between exposure to PAHs and development of HCC among smoker (OR=1.7). There was neither statistical significance nor positive association between exposure to PAHs and development of HCC among patients with chronic active hepatitis C (OR=0.6). There was a highly positive correlation between 1-hydroxy pyrene and Alfa Feto Protein (AFP) among positive cases of 1-hydroxy pyrene in case group (OR=316.25).

Recommendations:

Prevention programs aimed to elimination of exposure to PAHs is needed. Environmental monitoring of PAHs in different residential areas in different governorates for detection of source of pollution with PAHs in air, soil and water is needed. Further studies are needed to confirm the results of the present study.

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