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Study and Determination of Aryl Hydrocarbon Receptor with Some Trace Elements in Fuel Filling Station Workers

دراسة وتقدير مستقبل الأريل هيدروكاربون وبعض العناصر النزرة في عمال تعبئة محطات الوقود

Bassem Abd Al-Raheem Twaij[1*], Dr. Muthana Salam Mashkour[2],

Dr.Hussein Kadhem Al-Hakeim[2]

[1]Refinery of Najaf, Iraq.

[2]Department of Chemistry, Faculty of science, University of Kufa, Iraq.

[*]Corresponding Author E-mail: bassemtwij2@gmail.com

Summary

Pollution is the introduction of contaminants into the natural environment that cause adverse change. Gasoline is a toxic and highly flammable liquid consists of various types of aliphatic hydrocarbons, olefins, benzenes and aromatic hydrocarbons including toluene, xylene and a large number of volatile compounds in addition to tetraethyl lead. Gasoline consists of different types of aliphatic hydrocarbons, aryl compounds and some trace elements. Trace elements are several important roles in human bodies, some are essential for enzymes reactions where they attract and facilitate conversion of substrate molecules to specific end products. Aryl hydrocarbon receptor (AHR) is a receptor involved in the regulation of biological responses to planar aromatic hydrocarbons.

The aim of the present study is to compare the serum AHR level in the fuel station workers (FSW) with the non-workers as a control group. The other aim is to find out a possible correlation between AHR with trace elements.

Sixty male FSW and 30 controls, from ten fuel stations at Al-Najaf City-Iraq, were participated in the present study. The AHR level in serum was measured using ELISA technique. Determine the following metal ions Zn^{2+}, Cu^{2+}, Fe^{3+}, Mg^{2+}, Na^+ and K^+ level in filling station workers (FSW) and control group were measured spectrophotometrically by

using ready for use kits. Serum Pb level was carried out using Atomic absorption spectroscopy.

The results serum concentration of AHR in FSW group revealed a significant increase (p<0.001) as compared with the control group. No significant difference was noticed in AHR as compered in exposure ≥12years with exposure <12years in FWS. Smoking has no significant correlation with other parameters. Correlation study indicated a correlation between AHR and Age. Serum concentration of Cu^{2+}, Zn^{2+}, K^+ and Pb in FSW group revealed a significant increase (p<0.001) as compared with the control group. While Fe^{3+}, Na^+ and Mg^{2+} in FSW group revealed a significant decrease (p<0.001) as compared with the control group. Correlation study indicated a significant negative correlation between serum Pb and AHR while other trace elements showed no significant correlation with AHR in FSW group. There is a significant negative correlation between serum Cu^{2+} with age while there is significant increase correlation between Zn^{2+}, Mg^{2+} and Pb with age in FWS group.

Conclusion of study is The role of increase AHR on the health in FSW group, attention to use safety gloves and face mask is recommended for FSW and a long follow-up to the studied group is necessary to explore the   prognosis of increase AHR in FSW.

الخلاصة

التلوث هو دخول الملوثات الى البيئة الطبيعية التي تسبب تغيرًا سلبيًا. الكازولين هو سائل سام قابل للاشتعال يحتوي على انواع عديدة من الهيدروكاربونات غير الحلقية، الالكانات، الالكينات، البنزين والمركبات الحلقية التي تتضمن التلوين، الزايلين وعدد كبير من المركبات المتطايرة مضاف لها رابع اثيلات الرصاص. يتكون الكازولين من أنواع مختلفة من الهيدروكربونات الأليفاتية ومركبات الأريل وبعض العناصر النزرة.

العناصر النزرة هي الموجودة بتراكيز منخفضة جدا في سوائل الجسم، وهي ضرورية للحفاظ على الحياة و تشكل دور مهم لبناء الخلية رغم التراكيز القليلة، بعضها ضروري لتفاعلات الإنزيمات حيث تسهل تحويل جزيئات الركيزة إلى منتجات نهائية محددة. مستقبل اريل هيدروكاربون هو عامل استنساخ منشط يشارك في تنظيم الاستجابات البيولوجية للهيدروكربونات العطرية. الهدف من هذه الدراسة تحديد تركيز مستقبل اريل هيدروكاربون، وتحديد مستوى ايونات الخارصين، البوتاسيوم، الصوديوم، المغنيسيوم، الحديديك، النحاس والرصاص وإيجاد العلاقة بينهما للعاملين في تعبئة الوقود ومجموعة السيطرة (لغير العاملين). وقد شارك في هذه الدراسة ستون شخصا من العاملين في تعبئة الوقود، بالإضافة إلى ثلاثين من مجموعة السيطرة.

تم قياس تركيز مستقبل اريل هيدروكاربون باستخدام تقنية الاليزا وكذلك قياس مستويات ايونات الخارصين، البوتاسيوم، الصوديوم، المغنسيوم، الحديديك و ايون النحاس في مصل الدم باستخدام التقنية الطيفية و تحديد مستوى الرصاص باستخدام تقنية الامتصاص الذري.

أظهر تركيز مستقبل اريل هيدروكاربون في مجموعة العاملين زيادة معنوية (p<0.001) مقارنة مع مجموعة السيطرة. لم يلاحظ أي فرق معنوي في مستقبل اريل هيدروكاربون مقارنة لمدة التعرض ≥12 سنة مع مدة التعرض > 12سنة للعاملين. لم يكن هناك فرق معنوي (p>0.005) بين المدخن وغير المدخن للعاملين في كل المعاملات المقاسة. وجد علاقة ارتباط بين مستقبل اريل هيدروكاربون والعمر. أظهر تراكيز ايونات النحاس، الزنك، البوتاسيوم و الرصاص في العاملين زيادة معنوية (p<0.001) مقارنة مع مجموعة السيطرة. بينما ايونات الحديديك، الصوديوم و المغنسيوم اظهر انخفاض معنوي (p<0.001) للعاملين بالمقارنة مع مجموعة السيطرة. أشارت الدراسة إلى ارتباط سلبي كبير بين الرصاص و مستقبل اريل هيدروكاربون بينما أظهرت العناصر الأخرى عدم وجود ارتباط مع مستقبل اريل هيدروكاربون عند العاملين. كما أظهرت الدراسة علاقة سلبية كبيرة بين تركيز ايون النحاس والعمر في حين أن هناك زيادة معنوية بين الخارصين و المغنسيوم والرصاص مع العمر للعاملين. نستنتج من الدراسة وجود دور مهم لمستقبل اريل هيدروكاربون على صحة العاملين وضرورة استخدام الكمامات وقفاز اليد وضرورة الدراسة المستقبلية لمستقبل اريل هيدروكاربون.

Introduction

Air pollution is a complex mixture of gases, fumes and odors in amounts which could be harmful to human health or other ecosystems [1]. It is a well-documented fact that polluted air causes ill effect on the health, with urbanization and the rapidly increasing number of automobiles in most of the cities, there is an increase in air pollution. Exposed to organic and inorganic substances present in the oil [2]. Fuel station attendants to innumerous risks and health. The environment of fuel stations exposes gas hazards, which should be considered harmful to the health status of these workers [3]. There are chemical products to which these workers are exposed, such as aromatic hydrocarbons, benzene, toluene and xylene (BTX) components of gasoline and chemical solvents [4]. The chemical agent benzene, which posses a high risk to human health, even in small amounts, is a colorless, volatile, soluble, flammable liquid with high carcinogenic potential [5].

Gasoline may or may not be employed to initiate or propagate the spread of a fire. The American Society for Testing and Materials (ASTM) has a classification scheme for ignitable liquids including compositional carbon ranges and common peaks observed for each [6]. Gasoline components include various aliphatic (straight-chain) hydrocarbons, paraffins,

olefins, benzenes and aromatic hydrocarbons including toluene,xylene and a large number of volatile compounds with boiling points <80°C [7]. Over 300 different hydrocarbon molecules used in gasoline were observed to have boiling points ranging from 40°C to 190°C, showing that many components are highly volatile. Further classifications of the individual include the length of the carbon chain backbone, the extent of branching, and the isotopes of carbon atoms [8].

AHR is involved in normal cell physiology as well as xenobiotic metabolism, that AHR could be activated in the absence of xenobiotics [9]. AHR exists in cell cytoplasma in a complex with a heat shock protein 90 (HSP90). Dimer and a chaperone denoted X-assoeciatd protein 2(XAP2). When binding to an agonist (such as Polycyclic aromatic hydrocarbons PAHs), the AHR complex enters the cell nucleus where ARNT mediates HSP90 displacement, the formation of the AHR-ARNT heterodimer, which can bind to dioxin-responsive elements for AHR target-genes. Co-activators can be recruited by both AHR and ARNT, leading to transcription of a wide variety of genes [10].

Cytochrome P450 (CYP1A) is a primary target gene for AHR, and is almost totally dependent on AHR activity for expression. As shown in Figure this can result in formation of DNA and subsequent mutagenesis as CYP1A metabolizes various pro-carcinogens, like Benzo(a)pyrene (BaP) [11]. The classical mechanism for AHR activation in (Figure 1) results in the transcription of a number of target genes, including CYP1A [12]. By inducing the transcription of different biotransformation enzymes, AHR is a very important xenobiotic sensor. In addition, ligand Activated AHR also has the ability to interact and affect the functioning of other transcription factors, intracellular signaling pathways, cell proliferation, and the cell cycles [13].
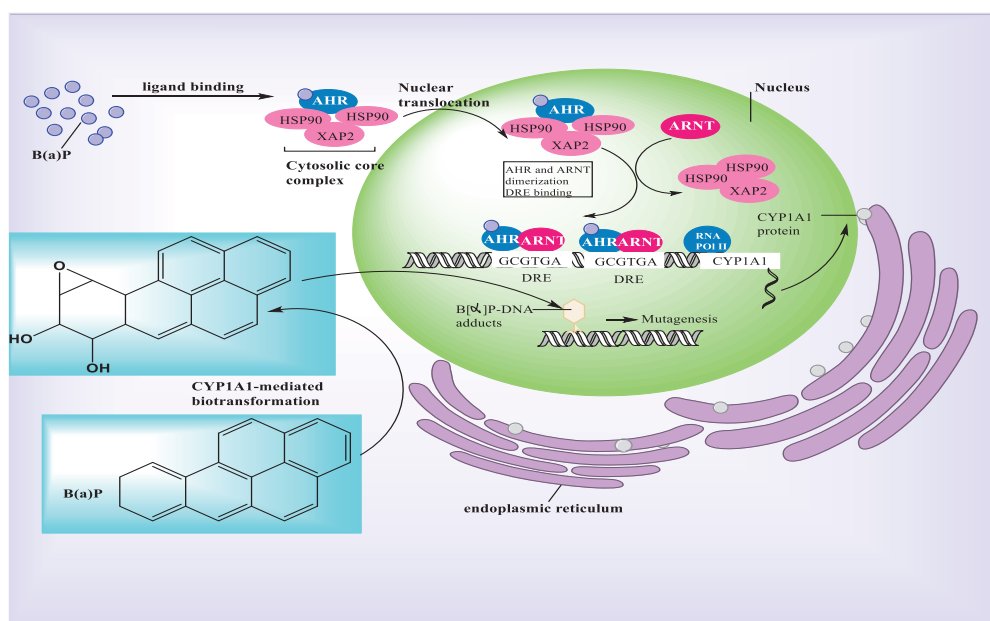
Fig. (1) Activation of AHR by benzo(a)pyrene (BaP). The cytosolic core complex AHR-HSP90-XAP2 enters,the cell nucleus after binding to an agonist. .ARNT mediates HSP90 displacement...and subsequent AHR-ARNT dimerization. CYP1A is a primary target gene for AHR, leading to formation of DNA and mutagenesis

Through the genome sequencing of many different species, it has become evident that AHR possesses an important physiological role beyond being a xenobiotic sensor [14]. The term trace element refers to a group of metals and metalloids that occur naturally in the ecosystem at low concentrations [15] and includes copper (Cu), iron (Fe) and zinc (Zn). Industrialization and urbanization increase the anthropogenic contribution of trace elements to the environment [16] , and as elements do not biodegrade [17] they consequently circulate in biogeochemical cycles within the environment [18].

Heavy elements such as lead, it is normal compound that is found in several forms including elemental, mineral, and organic [19]. Pb was used in various modern industries such as automotive industry, military, production of anti-corrosives, Pb salts as color stabilizer, battery production, and leaded gasoline. Workers in these industries are in direct exposure to lead [20].

The aims of the present study are study the level of AHR in serum of filling station workers (FSW) , to study the level of metal ions (Cu^{2+}, Fe^{3+}, K^+, Mg^{2+}, Na^+, Pb, and Zn^{2+}) in

serum of FSW and to study the correlation between level serum elements, and level of AHR in serum of FSW.

Materials and Methods

A-Patients: A blood samples were collected from 60 FSW males who work in fuel filling stations and exposed to different fuel derivatives for not less than 9 years (12.65±2.62 years). Their age range was (38.32± 6.12) years. Informed consent were obtained from all the participants. Questionnaires were precisely filled; candidates who met the criteria for participation in this study were enrolled in the study.The samples were collected from ten fuel stations located in Najaf city-Iraq.

B-Controls: Thirty healthy adults were selected as a control group. Their age range was apparently comparable to that of FSW (41.53±5.24 years).

 C- Exclusion Criteria: The study excluded any participant with chronic hypertension, diabetes Mellitus, autoimmune disease and renal disorder.

Measurements

Five milliliters of venous blood samples were drawn from each patient and control and were left at room temperature until complete clotting and then centrifuge at 3000 rpm for 5 minutes. Then Serum was separated and transported into three new disposable plain tubes and stored at -20 ºC till analysis. Serum level of AHR was measured by using ready for use ELISA kit supplied by Elabscience Co., USA. All other parameters metal ions Zn^{2+}, Cu^{2+}, Fe^{3+}, Mg^{2+}, Na^{+} and K^{+} level were measured spectrophotometrically by using ready for use kits, serum Pb level was carried out using Atomic absorption spectroscopy.

Statistical Analysis

The distribution types of the variables results were examined using Kolmogorov-Smirnov test. The normally distributed parameters were expressed as mean ± standard deviation. For the comparison between the patients and control groups, pooled t-test has been used. Pearson's correlation coefficients (r) were calculated to estimate the correlation between parameters. The difference between groups is considered as statistically different when $p<0.05$. All statistical analysis were performed using SPSS Statistics version 21 (2013), IBM-USA. While the figures constructed using Excel program of Microsoft Office 2010.

Results and Discussion

1- Comparison Study

1.1 Comparison between FSW and control

The comparison between FSW and control group are cited in Table (1).

Table (1) Comparison between FSW and control group

Parameter		Control	Patients	p-value
Age	year	39.53±5.24	38.32±6.12	0.012
Weight	Kg	82.57±12.01	80.70±12.69	0.498
AHR	ng/ml	2.37±0.73	3.85±1.73	<0.001
Cu^{+2}	ppm	1.06±0.07	1.22±0.09	<0.001
Zn^{+2}	ppm	0.95±0.05	1.05±0.05	<0.001
FeIII	μg/dl	122.90±9.96	96.28±13.91	<0.001
K^+	mmol/l	4.39±0.32	4.77±0.29	<0.001
Mg^{+2}	mg/dl	2.31±0.12	2.08±0.13	<0.001
Na^+	mmol/l	146.53±4.06	140.87±3.64	<0.001
Pb	μg/l	87.29±44.95	137.26±54.78	<0.001

There are a significant differences ($p < 0.001$) in the level of AHR between FSW (3.85±1.73 ng/ml) and control group (2.37±0.73 ng/ml). This result may be due to the stimulation of the receptors by gasoline and subsequent solublization and release of the receptors into the blood. Xenobiotic receptor is activated by planar lipophilic compounds such as polycyclic aromatic hydrocarbons and polyhalogenated aromatic hydrocarbons that present in the fuel, the latter group comprises polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans and dioxin-like polychlorinated biphenyls among others [21]. There is a significant increase in Cu (FSW 1.22±0.09 ppm and control 1.06±0.07 ppm, $p < 0.001$), Zn (FSW 1.05±0.05 ppm and control 0.95±0.05 ppm), K (FSW 4.77±0.29 mmol/l and control 4.39±0.32 mmol/l, $p < 0.001$) and Pb (FSW 137.26±54.78 μg/l and control 87.29±44.95 μg/l, $p < 0.001$) while There is a significant decrease in FeIII (FSW 96.28±13.91 μg/dl and control

122.90±9.96 μg/dl, p<0.001), Mg (FSW 2.08±0.13mg/dl and control 2.31±0.12 mg/dl, p<0.001) and Na (FSW 140.87±3.64 mmol/l and control 146.53±4.06 mmol/l, p<0.001).

Recent studies about the relationship between exposure to petrol products and the trace metal status, liver toxicity in gasoline filling workers reported that liver enzymes and serum levels of Cu, and Zn are increased concluding that long term exposure to petroleum products may increases risk of liver toxicity [22].

Chronic low level exposure to toxic metals is an increasing global problem. The symptoms associated with the slow accumulation of toxic metal are multiple and rather nondescript, and overt expression of toxic effects may not appear until later in life [23].

1.2 Comparison According to the Exposure Time of FSW

The comparison according to the exposure time of FSW group is cited in Table (2).

Table (2) Comparison according to the exposure time of FSW group.

Parameter		EXPOSURE ≥12years	EXPOSURE <12years	p-value
Age	year	39.23±6.06	36.50±6.00	0.105
Weight	Kg	82.35±12.81	77.40±12.08	0.156
AHR	ng/ml	3.98±1.83	3.58±1.52	0.366
Cu^{+2}	ppm	1.21±0.08	1.24±0.09	0.218
Zn^{+2}	ppm	1.05±0.05	1.04±0.05	0.512
FeIII	μg/dl	95.55±13.78	97.75±14.43	0.568
K^{+}	mmol/l	4.78±0.33	4.77±0.20	0.943
Mg^{+2}	mg/dl	2.10±0.12	2.04±0.14	0.125
Na^{+}	mmol/l	140.60±3.45	141.40±4.04	0.427
Pb	μg/l	133.30±62.71	145.16±33.87	0.346

The exposure time was divided into two categories; exposure time >12 year and exposure time<12 year. There is no significant difference between two categories of FSW group (p>0.05) in all the measured parameters. Long-term exposure to petroleum derivatives

increases the risk of liver and hematopoietic toxicity [24].Repeated or prolonged exposure to fuel products is more reflective of the occupational norm. Studies have shown that repeated dermal exposures to fuels result in skin irritation [25].

The healthy problems due to the long exposure to fuel derivatives depends on many factors such as concentration of the chemical substance and time of exposure. Contact with fuel vapors may be responsible for many diseases such as headache, nausea, and respiratory tract allergy [26] .
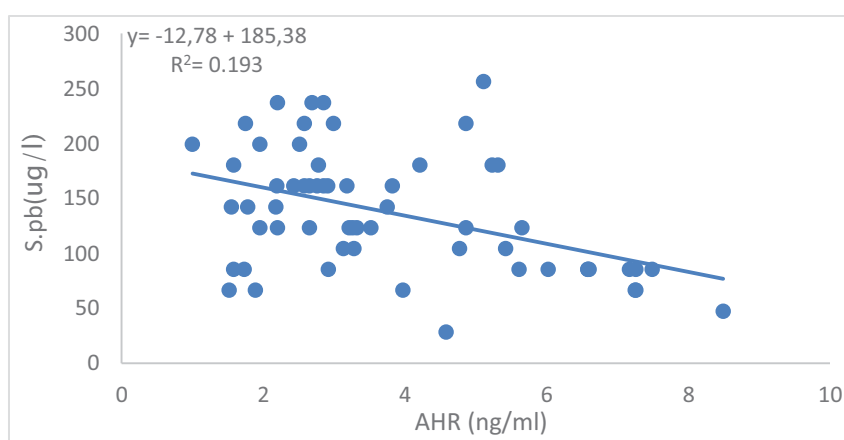
2- Correlation Study

2.1 Correlation between AHR & Trace Elements

The correlations between AHR and some trace elements in FSW group are cited in Table (3).

Table (3) Correlation between AHR & the parameters of some trace elements Tests.

		Cu^{2+}	Zn^{2+}	Fe^{3+}	Mg^{2+}	Pb	K^+	Na^+
AHR	ρ	-0.174	0.015	-0.133	0.201	-0.440	0.173	0.127
	p	0.183	0.909	0.313	0.123	0.014	0.187	0.334

There is a significant negative correlation (p=0.014) between serum Pb and AHR in FSW group (Figure 2). Other trace elements showed no significant correlation (p>0.05) with AHR.

y= -12,78 + 185,38
R^2= 0.193

Fig. (2) Correlation between Pb & AHR in FSW.

The present results are agreed with previous results where lead is a non-essential metal that is toxic to human tissue at very low concentrations [27] and is ranked second most toxic substance in the hazardous substances list by the Agency for Toxicity and Disease Registry [28]. The body burden of Pb increases with age, despite efforts to reduce exposure to the metal. The major sources of Pb are paints, water, food, dust, soil, kitchen utensils, and leaded gasoline. Most cases of Pb poisoning are attributable to oral ingestion and absorption .through the gut [29]. Most of the ingested Pb accumulates in specific   target tissues including blood, soft tissues, and bone, where it has a very long half-life[30]. Co-contamination with mixtures of PAHs and heavy metals, such as Pb, is a worldwide environment problem. These contaminants are co-released from different sources, such as car exhausts, tobacco smoke, and fossil fuel combustion [31]. Disruption of the AHR gene by Pb can affect the mutagenicity and carcinogenicity of PAHs and 2, 3,7,8-tetrachlorodibenzo-p -dioxin (TCDD) [32]. A number of modern studies have   investigated the crosstalk between heavy metals and AHR. For example, reported that cadmium induced the AHR-regulated gene in the rat small intestine and uterus [33].

2.2 Correlation between Serum Metals with Age and Weight

The correlations between serum metals with age and weight in FSW group are cited in (Table 4).

Table (4) Correlation between serum metals with age and weight in FSW

		Age	Weight
Cu^{2+}	ρ	-0.335	0.128
	P	0.009	0.329
Zn^{2+}	ρ	0.333	-0.022
	P	0.009	0.869
Fe^{3+}	ρ	-0.102	-0.088
	P	0.438	0.505
K^+	ρ	0.186	0.088
	P	0.092	0.506
Mg^{2+}	ρ	0.430	0.106
	P	0.001	0.421
Na^+	ρ	0.058	-0.096
	P	0.659	0.466
Pb	ρ	0.260	0.054
	P	0.047	0.683

There is no significant difference between serum metals and weight (p>0.05) while there is a significant difference between Cu^{2+}, Zn^{2+}, Mg^{2+} and Pb with Age (p=0.009, p=0.009, p=0.001, p=0.047).

A-There is significant negative correlation between serum Cu^{2+} and age in FSW group (Figure 3).
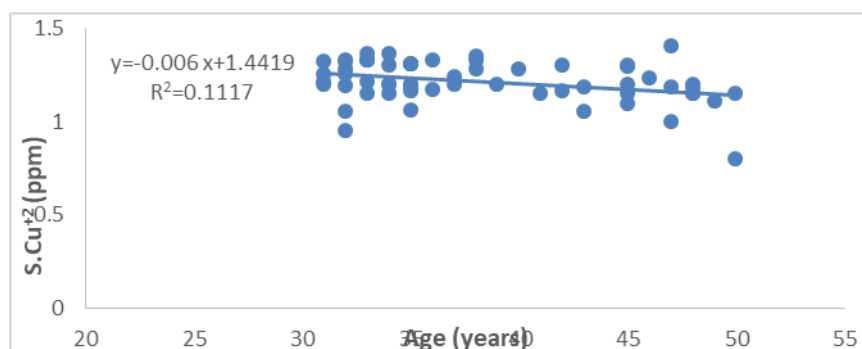
Fig. (3) Correlation between Cu^{2+}& Age in FSW.

The present results are agreed with previous results, Cu of the blood circulation is transported into the brain via the blood-brain barrier (BBB) and blood- cerebrospinal fluid (CSF) barrier[34]. Previous studies from those laboratory have demonstrated that the BBB serves as the major route for the transport of Cu into the brain parenchyma, while the blood-CSF barrier (BCB) mainly contributes to maintain the Cu homeostasis in the brain by exporting excess Cu from the CSF to the blood [35]. Once entering the brain, the Cu content and spatial distribution are uneven [36]. Age-related increase in brain Cu content was observed in mouse [37]. Other recent published study using X-ray fluorescent microscopy reveals an extraordinarily high Cu content in the subventricular zone along the wall of rat brain lateral ventricles, which appears to increase with age [38].

B-There is significant correlation between serum Zn^{+2} and age in FSW group (Figure 4).
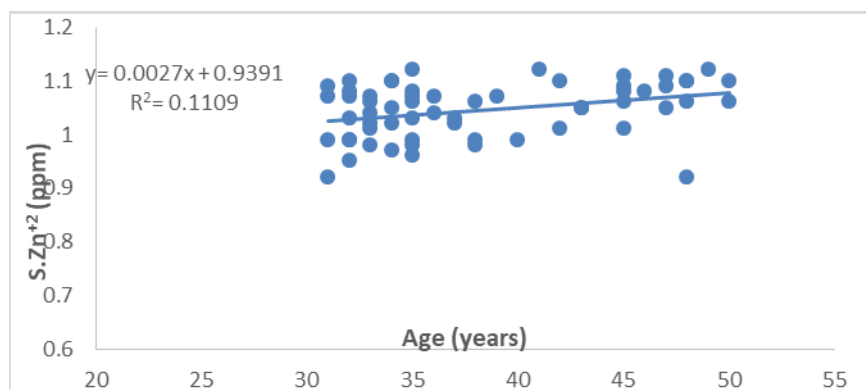
Fig. (4) Correlation between Zn^{+2} & Age in FSW.

The present results are agreed with previous results, the serum concentrations of Cu and Zn are strictly regulated by compensatory mechanisms that act to stabilize them within certain ranges of nutritional intake. However, there are mechanisms that are built to decrease serum concentration of Zn and to increase serum concentration of Cu in the presence of inflammatory conditions, so that a commons feature of several age-related chronic diseases is an increase of the Cu to Zn ratio (Cu/Zn) [39]. That during ageing, the intake of Zn decreases, thus contributing to frailty, general disability and increased incidence of age-related degenerative diseases [40].

C-There is significant correlation between serum Mg^{2+} and age in FSW group (Figure 5).
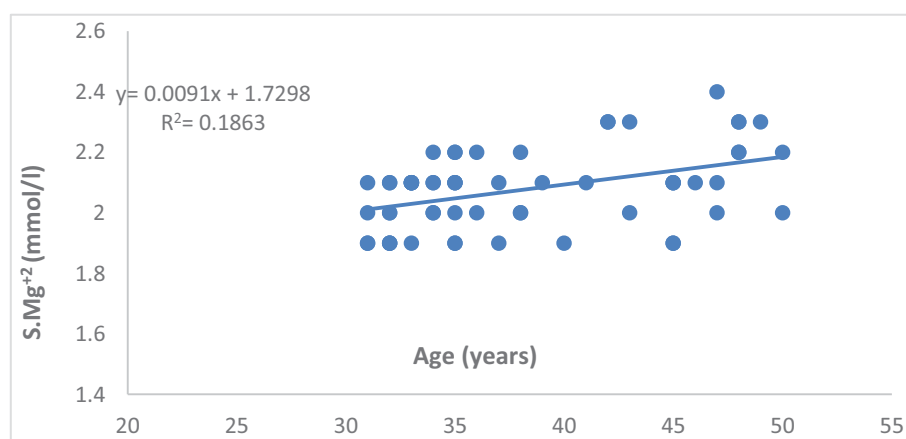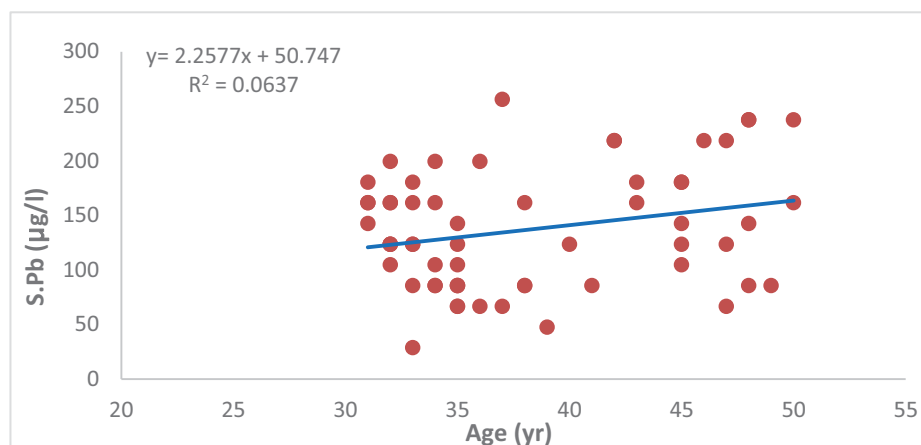

Fig. (5) Correlation between Mg^{2+} & Age in FSW.

The present results are agreed with previous results, our findings indicate that there are age-related differences in normal Mg concentration. Therefore ionized hypomagnesem should be defined on the basis of normative data for neonates, infants, children, and adults [41]. Older

adults have lower dietary intakes of Mg than younger adults [42]. In addition, Mg absorption from the gut decreases and renal Mg excretion increases with age [43]. Older adults are also more likely to have chronic diseases or take medications that alter Mg status, which can increase their risk of Mg depletion [44]. The population-based prospective of middle-aged Caucasian men that low serum Mg concentrations are independently associated with an increased risk of future total and femoral fractures. While serum Mg was observed a continuous decrease in risk of femoral fractures with increasing levels of serum Mg [45].

D-There is significant correlation between serum Pb and age in FSW group (Figure 6).

Fig. (6) Correlation between Pb & Age in FSW.

The present results are agreed with previous results, Pb is associated with a wide range of toxicity in children across a very broad band of exposures. These toxic effects extend from acute, clinically obvious, symptomatic poisoning at high levels of exposure and effects at lower levels. Pb poisoning can affect virtually every organ system in the body. The affected principal organs are the central nervous system and the cardiovascular, gastrointestinal, and renal [46]. Adults who are exposed to a dangerous amount of Pb can experience anemia, nervous system dysfunction, weakness, hypertension, kidney problems, decreased fertility, an increased level of miscarriages, premature deliveries, and a low birth weight of their child [47].

The role of Pb as an occupational pollutant stressor for elevated blood pressure could well be confounded by the presumed role of other risk factors such as age [48].

Conclusion

The present study shed a spot of light on the possible role of increase AHR in FWS group. The increase in serum AHR was associated with age in the FWS in comparing with the control groups. The level Cu^{2+}, Zn^{2+}, K^+ and Pb were increased in the FSW in comparing with the control groups. The increase in serum Zn^{2+}, Mg^{2+} and Pb were associated with age in the FSW. The decreased in serum Cu^{2+} was associated with age in the FSW. The increased in serum Zn^{2+}, K^+ were associated with increased Mg in the FSW. The level Fe^{3+}, Mg^{2+} and Na^+ were decreased in the FSW in comparing with the control groups.

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