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ORIGINAL ARTICLE

Liver Damage Risk Assessment Study in Workers Occupationally Exposed to E-waste in Benin City, South-South Nigeria

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KEYWORDS

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ABSTRACT: Large volumes of mostly irreparable electronic waste (e-waste) are shipped to Africa on a monthly basis, of which Nigeria receives the largest share. E-waste management practices in Nigeria have remained completely primitive until date; and e-waste workers have little or no occupational safety knowledge and devices. The thousands of chemicals in e-waste have been reported to be toxic to human health in any degree of exposure. The present study has assessed the risk of liver damage in workers occupationally exposed to e-waste in Benin City, South-south Nigeria in 2014. Serum activities of liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP)]; and levels albumin (ALB), total bilirubin (T/Bil) and conjugated bilirubin (C/Bil) were determined using standard colorimetric methods. Serum Alpha fetoprotein (AFP) was determined using ELISA in Nigerian e-waste workers (n=63) and in age-matched unexposed participants (n=41) in Benin City. The results showed significantly raised activities of enzymatic biomarkers of liver damage (ALT, AST, ALP and GGT) in the e-waste group compared with the unexposed participants. There was no significant difference in the levels of ALB, T/Bil and C/Bil between exposed and unexposed participants. AFP levels in e-waste workers (3.56 ± 0.34 ng/mL) were

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significantly different compared with the unexposed group (2.14 ± 0.80 ng/mL) ($P< 0.045$). The significantly elevated cancer risk biomarker (AFP) and the enzymatic biomarkers of liver damage observed in the Nigerian e-waste workers studied may be associated with occupational exposure to known carcinogens and hepatotoxic metals in e-waste.

INTRODUCTION

The invention of electricity has revolutionized technology in the recent years and advancement in technologies have led to the invention and manufacturing of many electrical and electronic equipment. Rapid economic growth, coupled with urbanization and a growing demand for consumer goods has led to increased production of electronics [1].

Large volumes of electrical and electronic equipment with most of its components toxic and non-biodegradable are made with short life span hence discarded as waste, thus making e-waste the fastest growing waste stream globally [2].

Africa as a continent has been battling with environmental challenges especially issues of chemicals and wastes, which are on the ascendancy with crosscutting impacts. The magnitudes of which are yet to be fully assessed and recognized, bearing in mind the connection between waste, climate change and human health [3].

Electronic waste (e-waste), e-scrap, or waste electrical and electronic equipment (WEEE) describes discarded electrical or electronic devices. This includes items such as obsolete personal computers (PCs), laptops, television, monitors, refrigerators, fax machines, cell phones, batteries and consumer electronics among others [3]. Electronics, which are destined for, reuse, resale, salvage, recycling, or disposal may also be term e-waste [4].

The primitive processing of electronic waste in developing countries may lead to remarkable health and pollution problems [4]. E-waste contains over 1,000 chemicals, including polychlorinated biphenyls, tetrabromo-bisphenol-A, chlorofluorocarbons, polyvinylchloride, phthalates and its derivatives, dioxins, furans and potential toxic metals such as lead, cadmium, chromium, mercury, copper, manganese, nickel, arsenic, zinc, iron and aluminium [5].

Greenpeace, a global Environmental Protection Agency in a publication highlighted that e-wastes contain such health-threatening substances as mercury, lead, arsenic, cadmium, berylium, hexavalent chromium, bromated flame retardants (BFRs), polyvinyl chloride (PVC); as well as phthalates (phthalate esters) and Organotins [6,7]. Some of these substances are known potential hepatotoxicants [6, 8].

In Sub-Saharan African countries, the trade of e-waste has been declared hazardous and illegal based on the provisions of the Bamako Convention, notwithstanding, it has continued to grow remarkably in Nigeria. Although Nigeria ratified the Basel Convention on May 24, 2004, it still has not ratified the Bamako Convention, and the country remains a dumping ground for e-waste from European and Asian markets [9, 10]. It is reported that about 500 containers of second-hand electronics are imported to Nigeria on a monthly basis from Europe, and each is estimated to contain about 500 computers, of which about three-quarters are often verified to be junk and non-reusable[11, 12]. Expectedly, this non-reusable WEEE is dumped in domestic landfills.

Humans can become exposed to toxic metals in dust through several routes, which include ingestion, inhalation, and dermal absorption [13-15]. In dusty environments, adults could ingest about 100 mg dust/day [14, 17, and 18]. Exposure to high levels of toxic metals can result in acute and chronic toxicity, such as injury to the human brain and nervous system

[18]; distress the kidneys [19-21], birth defects [22, 23] and even death. The Minamata disease in Japan between 1954 and 1965; the Love Canal incident, near Niagara Falls in the US; the Koko incident of 1988 in Nigeria; the Zamfara lead poisoning in Nigeria; the Thor Chemicals diseases of the early 1990s in South Africa; the disastrous dumping of hazardous wastes incident in Ivory Coast, in 2006, are among the numerous pointers to the grave consequences that unscrupulous waste dumping could have on human beings, jeopardizing their livelihood, liberty and very existence.

With the unregulated heavy inflow of e-waste into Nigeria, the risk factors and occupational lifestyle of e-waste workers, coupled with other widespread health-threatening pollutions, the development of hepatocellular disorders is not impossible. There is a remarkable association between toxic metals and liver parenchymal cell damage; some metals being known to be potential hepatotoxicants [8].

Liver dysfunction or necrosis has been reported to be associated with overload of toxic metals, drugs and other xenobiotics [24]. The theory of hepatotoxicity centers on the central role played by the liver in biotransformation and disposition of xenobiotics [25-27]. Injury to the parenchymal cells of the liver may arise from oxidative stress due to interaction with toxic metals. Cadmium, lead and arsenic are known to generate reactive oxygen species such as $O_2^{\cdot}$ H_2O_2 and $^{\cdot}OH$ that cause oxidative stress [28, 29]. Iron and copper may be replaced by cadmium from a number of cytoplasmic and membrane proteins like ferritin. This may lead to increase in the concentration of iron and copper ions, thereby initiating oxidative stress through Fenton reaction [30].

Oxidative stress generated by these toxic metals may cause increased generation of reactive oxygen species, which in turn causes lipid peroxidation of important biomembranes. These species may interact with biological macromolecules and lead to DNA damage as well as its hypo- or hyper-methylation. In the overall consideration, there may be alterations in regulatory mechanisms of cell proliferation and eventually cell death [31]. Toxic metals such as lead and cadmium displace trace element in antioxidant enzymes and vital biomolecules and disrupt their activities [32]. For instance, zinc in superoxide dismutase, selenium in glutathione peroxidase is replaced by lead thereby deactivating them and depleting the glutathione store, hence an increased chances of lipid peroxidation through oxidative stress on biomembranes [33, 34]. Hepatic cellular dysfunction and death initiate immunological reaction that triggers off signals, which activates the kupffer cells and natural killer cells. These cells release proinflamatory mediators such as interkeukins, interferon-gamma and tissue necrotic factors. These cytokines attract more inflammatory cells causing injury to the liver [35].

Based on the theory of metal induced hepatotoxicity, the present study aimed at assessing the risk of liver damage in Nigerians occupationally exposed to toxic metals in e-waste.

MATERIALS AND METHODS

Study Design

This research was designed as a comparative study between occupationally exposed and non-exposed subjects.

Study Area

This study was carried out in the Metropolitan City of Benin, Edo State formerly Mid-western but now South-south Nigeria in 2014. Benin City is the current capital of Edo State with an estimated average population of 1,147,188 in the 2006 general census.

Study Population

Exposed Subjects

Male Waste Electric and Electronic Equipment (WEEE) Workers (n =63, Mean age of 31 years) working and living in Benin City, formed the exposed group. The states of origin of the exposed subjects comprised of Edo, n=32 (50.8%); Imo, n=15 (23.8%); Delta, n=7 (11.1%); Anambra, n=3 (4.8%); Ekiti, n=2; (3.2%); Enugu, n=2 (3.2%) and Abia, n=2 (3.2%). Only subjects with a minimum of 5 years of occupational exposure to toxic substances in WEEE were enrolled into the study.

Unexposed Subjects

Age-matched apparently healthy male participants (n = 41), with minimal or no occupational exposure to toxic substances in WEEE, recruited from the Ugbowo Campus Community of the University of Benin formed the unexposed group in this study.

Inclusion Criteria

a) Exposed subjects comprised of Electronic Technicians carrying out informal (primitive) e-waste recycling, processing, repair and dismantling repair of electronic and electrical equipment. Subjects who were occupationally exposed to e-waste for a period of five years and above at the time of sample collection were considered suitable for the study.

Five years duration of exposure is based on Electronic Waste Risk Assessment Report of Adaramodu [36].

b) Control subjects were apparently healthy male individuals with minimal or no occupational exposure and with no hobby involving e-waste exposure. The unexposed participants had no previous demographic and medical history of incidence of cancer.

Exclusion Criteria

E-waste workers who were not exposed to e-waste for a period up to five years at the time of sample collection were not considered suitable for the study. Subject with history of any form of cancer, tobacco smoking and alcoholism were excluded from the study. Tobacco smoking and alcohol consumption also served as basis of exclusion in the recruitment of the apparently healthy control subjects.

Ethical Approval

The protocol for this study was approved by the Health Research Ethics Committee of University of Ibadan/University College Hospital, Ibadan, Nigeria (UI/UCH EC Registration Number: NHREC/05/01/2008a)

Informed Consent

Subjects for this study were adults who were adequately briefed on the research protocol and informed consent was obtained prior to sample collection. The informed consent form contents were explicitly explained to the participants in English and in their local dialect.

Sample Collection

Approximately 5 ml of venous blood was collected from test subjects (e-waste workers) and control subjects using standard phlebotomy techniques. Blood samples obtained were dispensed into plain (anticoagulant-free) specimen bottles to obtain serum after clotting and centrifugation at 3000 revolution per minute for 3 minutes. Analysis of samples for the generation of research data was carried out using the well-preserved and labeled samples.

Laboratory Analysis

The serum activities of the liver enzymes (ALT, AST and ALP) were estimated using a well calibrated

Reflotron chemical analyzer, which applies reflectance photometry principle in its operation. Gamma-glutamyl transferase was estimated using diagnostic kits manufactured by Randox Labs, United Kingdom, based on the colorimetric method described by Szasz [37]. Serum albumin concentration was determined using Bromocresol Green method. Total and conjugated bilirubin levels were determined using diagnostic kits manufactured by Randox Labs, United Kingdom, based on the colorimetric method described by Jendrassick and Grof, [38]. Concentrations of Alpha-fetoprotein in the samples were estimated by ELISA [39, 40].

All biochemical assays were carried out in the Clinical Chemistry laboratory of the Department of Medical Laboratory Science, University of Benin, Benin City.

STATISTICAL ANALYSIS

Statistical analyses including descriptive statistics were carried out using the Statistical Package for Social Scientists (SPSS) version 16.0 (Chicago, IL, USA). All values were expressed as Mean ± Standard Error of the Mean. The Independent Student's *t*-test was used to determine significant differences between exposed and unexposed groups and P value < 0.05 was accepted.

RESULTS

Enzymatic biomarkers (ALT, AST, ALP and GGT) of liver damage in Nigerian e-waste workers and unexposed participants are shown in Table 1.

The levels of (ALT, AST, ALP and GGT) in e-waste workers were significantly different from the unexposed group.

The biosynthetic function and biotransformation function of the liver as indicated by serum albumin, total bilirubin and conjugated bilirubin are presented in Table 2. As indicated, levels of serum albumin, total bilirubin and conjugated bilirubin between the exposed and unexposed participants showed no significant difference (P> 0.05).

Table 1 Enzymatic Biomarkers of liver Damage in e-waste exposed and unexposed participants

Variables	Exposed Participants (n=63)	Unexposed Participants (n=41)	Degree of Freedom	*P* value	Level of significance
ALT (U/L)	24.39 ± 1.30	18.05 ± 1.24	101	<0.01	Highly significant
AST (U/L)	37.36 ± 1.42	23.54 ± 1.34	101	<0.001	Highly significant
ALT (U/L)	82.84 ± 2.47	82.84 ± 2.47	101	<0.001	Highly significant
GGT (U/L)	0.05 ± 0.01	0.02 ± 0.00	71	0.019	Significant
De Ritis Ratio	1.531	1.304			
(AST/ALT)	Ratio= 1.2				

Note: Values in *Mean ± Standard Error of the Mean*

Table 2. Assessment of Biosynthetic and Biotransformation Function of the Liver in e-waste exposed and unexposed group

Variables (mg/dL)	Exposed subjects(n=63)	Unexposed subjects (n=40)	Level of significance
Albumin	4.76±0.03	4.86±0.06	Not significant
Total Bilirubin	0.61±0.04	0.53±0.07	Not significant
Conjugated bilirubin	0.36 ±0.03	0.31±0.03	Not significant
Unconjugated bilirubin	0.25±0.02	0.33±0.05	Not significant

Note: Values in *Mean ± Standard Error of the Mean*

DISCUSSION

Enzyme markers are better indicators of the status of an organ. The liver enzymes (e.g. alanine transaminase, aspartate transaminase, alkaline phosphatase and gamma-glutamyl transferase) have very low serum concentration [41, 42]. The alanine aminotransferase (EC2.6.1.2) is found primarily in the liver with trace amount in skeletal muscles and heart. It is found in the cytoplasm and mitochondria where it is involved in protein metabolism. It leaks out of damaged tissues in hepatocellular necrosis [43, 44]. AST (EC2.6.1.1) is an enzyme found in both mitochondrial and cytoplasmic compartments of the cell. The reductive transfer of an amino group from aspartate to α-ketoglutarate resulting in the yield of oxaloacetate and glutamate is catalyzed by AST. It also leaks out into the serum during hepatocellular necrosis [45, 46]). ALP (EC3.1.3.1) and γ-GT (2.3.2.2) are membrane bound glycoprotein enzymes. Their elevated plasma concentration is due to hepatobiliary injury and cholestasis [27, 47, 48, and 49]. In the event of damage to the parenchymal cells of the liver, these enzymes leak from the intracellular compartments into the serum resulting in elevated serum concentrations. Some investigations [50-53], showed that toxic metals (including cadmium, mercury, arsenic and others) are hepatotoxic. Arsenite intoxication of rat induced hepatocyte membrane damage causing leakage of ALT, AST and ALP into circulation as well as causing focal necrosis in the liver [54].

The present study has shown a marked elevation of serum concentration of these enzymes in the exposed subjects compared to the non-exposed subjects which are statistically significant at $P<0.05$. This may have resulted from interaction of toxic metals with the parenchymal cells of the liver, which may have resulted in necrosis. This is in consonance with the work of Lee et al. [55], Mahour and Saxena [56] where marked elevation of serum activities of liver enzymes were observed in rats intoxicated with toxic metals. Elevation of serum activities of liver enzymes was also observed by Jagadeesan and SankarsamiPillai, [57] in albino rats intoxicated with $HgCl_2$.

Hepatic functions, biosynthetic ability and integrity of hepatocytes are affected by the deleterious effects of toxic metals. In liver disorders, total protein and albumin are observed to decrease due to reduced number of hepatocytes and impaired function [57-59]. In liver cirrhosis, all liver synthesized proteins decrease while globulin increases due to imposed kupffer cell function and acute phase protein production.

However, the liver has significant reserve capacity to maintain protein concentration. This can only fall in extensive liver damage. Many liver proteins have long half-life. For instance, albumin has a half-life of three weeks. The rate of decreased protein synthesis in the liver depends on the type, severity and duration of liver injury. In acute hepatic dysfunction, there is little or no change in the total plasma protein concentration [60].

This study has shown that the serum concentration of albumin in Nigerians occupationally exposed to e-waste has been reduced compared with unexposed group, the difference was however not significant.

This may be because hepatocytes, which synthesize these proteins, have a minimal turn over and a lifespan of about one year [61]. The liver can loss its function only when a larger portion has been destroyed or removed. For instance, in liver transplant, liver failure occurs when about 20-25% is left and fails to regenerate [62-64], observed that liver has the ability to regenerate itself after an assault or surgical removal of its part. This stimulated hepatocytes proliferation leads to the gradual restoration of the liver mass through a process of compensatory hyperplasia. The regeneration of liver cells from its oval (progenitor) cells could be a reason for the undetected reduction in the biosynthetic function

of the liver [65, 66, and 67]. In addition, the liver increases the production of positive acute phase proteins than negative acute phase proteins during inflammation of its cells [68].

The liver also conjugates indirect bilirubin from erythrocytes destruction in the reticulo-endothelial system. Bilirubin is transported to the liver bound to albumin. It is taken up by the hepatocytes, which conjugate them to bilirubin diglucuronide by the action of uridyl diphosphate glucuronyltransferase enzyme. This enables the renal excretion of bilirubin. Injury to the hepatocytes results in increased total bilirubin. Diseases and assaults on the hepatocytes may reduce the conjugating function of the liver. More so, any obstruction to the bile canaliculi can as well cause an increase in serum bilirubin.

Venkatesan and Sadiq observed an elevated serum bilirubin in rats exposed to mercury intoxication [69]. In another study, using animal model, Mohamed et al., [70] observed an increased serum level of total bilirubin because of mercury intoxication. Cadmium caused an elevated bilirubin level along with ALT, AST, ALP and γ-GT [71].

However, in this study, the mean values for Total bilirubin (TB) and Conjugated bilirubin (CB) were slightly higher (not significantly different) in exposed subjects compared with unexposed subjects. Increase in both TB and CB in the exposed subjects may be because of haemolytic processes, which may be secondary to erythrocyte membrane lipid peroxidation. It has been reported that some metals such as gold, mercury, copper and lead (part of WEEE) cause lipid peroxidation [71, 72]. Increased release of haemoglobin from haemolysis of erythrocytes explains the higher values of the two forms of bilirubin in the exposed subjects.

The insignificant differences observed in the serum albumin, total bilirubin as well as conjugated bilirubin in the exposed participant studied compared with the non-exposed is an indication that the biosynthetic capacity and biotransformation function of the liver of Nigerians occupationally exposed to e-waste was not or has not been affected. However, the marked elevation of serum activities of liver enzymes is an indication that the liver may be undergoing necrosis because of interaction of the liver cells with toxic metals in waste electrical and electronic waste.

De Rittis ratio (1.2) obtained revealed that the damage to the liver was not a result of alcoholism. This observation is supported by the work of Moussavian et al. [73] on influence of alcohol ingestion and liver disease. They established that an AST to ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease, particularly in the setting of an elevated gamma-glutamyltransferase.

AFP value (3.56± 0.34ng/mL) in e-waste exposed group was within the reference range of (3.04 ± 1.9ng/mL) in healthy population. Howbeit, this value was significantly higher than the mean AFP levels in the unexposed group (2.14± 0.38ng/mL).

Previous report demonstrated histopathological changes in liver of fish exposed to a wide range of heavy metals [75]. The value of testing for alpha-fetoprotein (AFP) for the diagnosis of primary hepatocellular carcinoma is well established [74, 75]. The body has limited capacity to respond to cadmium exposure, as the metal cannot undergo metabolic degradation to less toxic species and it is only poorly excreted, making long term storage (especially in the liver) a viable option for dealing with this toxic element [73]. The increased AFP level in the exposed subjects of this study may be associated with the promotion of oxidative stress by liver-stored heavy metals, of which cadmium is a culprit being reportedly stored in the liver [73]. The oxidative stress stimulated in the liver by the accumulated heavy metals may cause DNA damage, which may exacerbate cellular proliferation in the liver. The increased level of AFP may be attributed to this cellular proliferation.

In addition, AFP reactivation in adults may result from liver regeneration, noncancerous liver diseases such as viral hepatitis or cirrhosis, primary liver or germ cell tumors and to lesser extent several forms of other epithelial malignances [76]. The liver has regenerative ability; destruction of hepatocytes in heavy metal toxicity by oxidative stress will lead to stimulation of regeneration of hepatocytes, which will consequently lead to increase in AFP as the expression of AFP gene is increased during growth, and regeneration of the liver cells. This may have accounted for the higher AFP values obtained in the e-waste group.

In addition, AFP has been localized in the cytoplasm of hepatocytes, thus increased destruction of hepatocytes in heavy metal toxicity will reflect an increased level of serum AFP [76].

Thus, the rising AFP levels in the exposed participants of this study may be associated with the pathobiology of metal-induced hepatotoxicity in chronic occupational exposure.

CONCLUSIONS

Significantly elevated cancer risk biomarker (AFP) and the enzymatic biomarkers of liver damage observed in the Nigerian e-waste workers studied may be associated with long-term occupational exposure to known carcinogens and hepatotoxic metals in e-waste. A trend towards hepatocellular damage in the e-waste exposed workers appears to be indicated. Use of personal protective devices and monitoring the status of AFP and liver enzymes in Nigerian e-waste workers would be immensely useful in evaluating exposure risk.

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