A NEW ETHICAL DILEMMA FOR HEMODIALYSIS PATIENTS : EXPOSURE TO DIETHYL HEXYL PHTHALATE

BY

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ABSTRACT

Patients undergoing hemodialysis are exposed to medical devices containing di-ethylhexyl phthalate (DEHP). There is an ongoing discussion about the risks of DEHP exposure for the general population as well as for specific subgroups in various medical settings. Due to the widespread use of DEHP in polyvinyl chloride (PVC) medical devices and in life, this work is an essential step in such a way that the exposure amount of DEHP would be precisely determined in patients undergoing regular hemodialysis in order to evaluate its significance as an integral part of the assessment of the risk of DEHP to human liver. Thirty subjects were involved in this work. Ten of them were healthy volunteers (n=10) as a control group and twenty patients with end stage renal disease (ESRD) on regular hemodialysis (n=20). Two samples were taken from all subjects, one prior to and one after the dialysis session, for measuring the serum levels of: alanine transaminase, aspartate transaminase and albumin, and the estimation of DEHP serum level by using high performance liquid chromatography (HPLC). Significant increases ($p<0.001$) were detected in DEHP mean serum levels between postdialysis samples and control samples on one side, and predialysis samples on the other side. There is a continuous exposure to DEHP in hemodialysis patients, where they would be considered of the target vulnerable groups continuously exposed to DEHP in high amounts. The shift towards safer PVC-free or DEHP-free alternatives should be evaluated and encouraged.

KEYWORDS: *Bioethics, DEHP, Serum, HPLC, Hemodialysis.*

INTRODUCTION

As a chronic illness, end-stage renal disease (ESRD) occurs when the kidneys are no longer able to function at a level needed for day-to-day life. This usually occurs when chronic kidney disease has worsened to the point at which kidney function is less than 10% of normal (Al-Ghamdi et al., 2010), hence starting the renal replacement therapy via dialysis or renal transplantation (Checherita et al., 2010).

Patients undergoing hemodialysis are exposed to medical devices containing di-(2-ethylhexyl) phthalate (Schettler, 2006).

Di(2-ethylhexyl) phthalate (DEHP, also is referred to as DOP i.e. Di-octyl Phthalate) is the major plasticizer used in polyvinyl chloride products to achieve the desired softness and stability for the required applications (Wahl et al., 2004).

Plasticized PVC material possesses numerous advantages which makes it the material of choice for medical and, more particularly, for blood contact applications (Hildenbrand et al., 2005), where it may constitute up to 40% by weight (Wahl et al., 1999). Di(2-ethylhexyl) phthalate, used in the compounding of PVC, is mainly responsible for building-in the desirable characteristics of medical applications, such as transparency, flexibility, strength, elasticity, stability at low and high temperatures, permeability to water, oxygen and carbon dioxide in the desired range (Hildenbrand et al., 2005).

Medical devices with the highest DEHP content include dialysis tubings, infusion sets and storage bags for blood, parenteral nutrition and continuous ambulatory peritoneal dialysis (CAPD) fluids (Wahl et al., 1999). Since DEHP is not chemically bound in the plastics, it can be leached to the environment during the manufacturing process and product use and after disposal (Wahl et al., 2004).

DEHP produces a wide spectrum of toxic effects in animals and multiple organ systems including the liver, reproductive tract, kidney, lung and heart (Doull et al., 1999). Several studies noticed the existence of DEHP or its metabolites in the blood, tissues, or urine of patients following treatment with PVC medical devices, as a result of leaching processes, with possible serious medical complications (pulmonary insufficiency, pulmonary edema, testicular atrophy and liver cancer) (Dickerson, 1997).

Hemodialysis, for treating end-stage renal disease, affects many aspects of a person's life, where problems faced by this may include not only physical impairments, but also restrictions in daily activities, a negative body perception, decreased self sufficiency, work restrictions, and social stigmata. In a sense, ESRD patients is cursed with 'misfortune', thus, how is such a person going to live a good life? (Dekkers et al., 2005).

This work is an essential step in such a way that the exposure amount of DEHP would be precisely determined in patients undergoing regular hemodialysis in order to evaluate its significance as an integral part of the assessment of the risk of DEHP to human liver.

SUBJECTS AND METHODS

SUBJECTS

The following study was approved by the local Ethics Committee and informed

consent was obtained from all subjects. A randomized controlled study was conducted on 30 participants. Ten of them were control healthy volunteers (n=10), who were not exposed to any of the DEHP containing medical devices. The remaining 20 participants were patients undergoing regular hemodialysis therapy in nephrology department, Zagazig University Hospitals, Egypt. They were grouped into: patients undergoing regular hemodialysis therapy from 6 months till 5 years (n=10), and patients undergoing regular hemodialysis therapy for 6-10 years (n=10). Patients with associating liver or cardiac diseases were excluded from the study.

Each patient underwent dialysis for a 3 hours period, three times weekly with a double needle access in arterio-venous fistulas using a membrane dialyzer (Polysulfone dialyzers) and a single-pass dialysate delivery system with a constant dialysate flow rate of 500 ml/min (Stankuviene et al., 2010).

Two blood samples were drawn from each hemodialysis patients. The 1st was prior to dialysis and the 2nd was after the dialysis session.

METHODS

Chemicals

(1) Diethylhexyl phthalate (DEHP) standard (MW 390.57) was purchased from Sigma-Aldrich (Milan, Italy).

(2) Chemical reagents of mobile phase (phosphoric acid and acetonitrile) were purchased from Merck (Darmstadt, Germany). All the chemicals and solvents were of HPLC reagent grade.

Sampling :

Venous blood samples were withdrawn from all subjects before and after dialysis and collected in glass tubes, allowed to clot at room temperature and then samples were centrifuged at 3000 rpm. Clear sera were separated into a small glass tube and stored at -20 C^o until time of analysis.

Chemical Analysis :

1- Liver function tests :

Predialysis liver function tests were performed as a routine investigation for patients undergoing hemodialysis therapy in nephrology department, Zagazig University Hospitals, Egypt. Colorimetric method was used in the estimation of alanine transaminase (ALT), aspartate transaminase (AST) (Reitman and Frankel, 1957) and serum albumin (Hunt and Lehmann, 1960).

2- DEHP serum level

Diethylhexyl phthalate can be estimated in the serum using different techniques as High - Performance Liquid Chromatog-

raphy (HPLC) (Kenny and Ahmad, 1993; Koo and Lee, 2007). Determinations of serum DEHP using High Performance Liquid Chromatography (HPLC) was carried out according to method described by Giam et al. (1978), with the use of UV/ visible spectrophotometer detector (Model LC 290, Perkin Elmer). Ultraviolet detector was set at different wavelengths and a wavelength 270nm was selected as it gives the maximum absorption of standards. All sample peaks were identified on the basis of their retention times for comparison, with the standard compounds. The retention time of DEHP was observed to be 12.28 min.

Analytical Procedure :

Instrument (HPLC) used was Perkin Elmer model LC 1020 plus, carried out on a gradient pump (Binary LC pump 250), a model LC1210 UV/Vis detector. A model LC1610 Auto Sampler (Australia, GBC Scientific equipment , Pty Ltd.) and LC 18 column (particle size 3 µm, 3 cm x 4.6 mm inner diameter, Supelco Inc., Supelco park, Bellefonte, PA USA). The mobile phase consisted of a mixture of acetonitrile and 0.1% H3PO4 (pH 3.0) (90:10, v/v). The mixture was prepared daily before use and delivered at a flow rate of 1.0 ml/ min. Column eluate was monitored at 270 nm. Stock solutions containing DEHP or MEHP (2 mg/ml) were prepared by dissolving a weighed amount of substance in acetonitrile.

Standard solutions were prepared by dilution of the above stock solutions with mobile phase and by varying the concentration in the range 0.05–5 µg/ml (Figures 1a-f).

The calibration curves for HPLC analysis were obtained by plotting peak areas versus concentration. The equations, obtained through regression analysis of data for the above standard solutions (six data from average of a minimum number of five determinations). A total 200 µl of plasma was added to 400 µl NaOH 1 mol/l, 100 µl 50% H3PO4 and 600 µl acetonitrile. After each addition, the sample was shaken by vortex for 30 s. After centrifugation for 10 min at 1500 g, the supernatant was separated and the residue was again extracted with 600 µl acetonitrile. After repeated centrifugation, the supernatants collected were evaporated, reconstituted with 400 µl of mobile phase and injected into the chromatograph.

Statistical Analysis :

For statistical analysis, SPSS 13.0 for windows programme was used. The data were expressed as mean ± SD. P values <0.05 were considered to be significant. Significant difference between groups was calculated by Student-t test. The Spearman correlation test was used to test the relationship between serum DEHP level and the duration of dialysis, and the relationship between serum DEHP level and

serum albumin. The level of significance for correlation test was carried out at 0.05 level, where p >0.05 (NS) and p <0.05 (significant correlation: r*).

RESULTS

Demographic characters of the involved subjects

Age, and sex of the involved subjects are represented in table(1).

Liver function tests

Significant increase ($p<0.01$) in the mean serum liver enzymes levels and a significant decrease ($p<0.01$) in the mean serum albumin level were recorded between patients undergoing regular hemodialysis therapy from 6 months till 5 years (67.78 ± 0.92 units, 53.05 ± 2.1 units and 3.7 ± 0.48 g/dL, respectively) and the control group (29.45 ± 2.1 units, 15.04 ± 1.7 units and 6.8 ± 1.73 g/dL, respectively) (Table 2, Figures: 2 & 3).

Significant increase ($p<0.001$) in the mean serum liver enzymes levels and a significant decrease ($p<0.001$) in the mean serum albumin level were recorded between patients undergoing regular hemodialysis therapy from 6 - 10 years (86.91 ± 2.31 units, 71.62 ± 2.7 units and 2.50 ± 0.63 g/dL, respectively) and the control group (29.45 ± 2.1 units, 15.04 ± 1.7 units and 6.8 ± 1.73 g/dL, respectively) (Table 3, Figures : 2 and 3).

Significant increase ($p<0.05$) in the mean serum liver enzymes levels and a significant decrease ($p<0.05$) in the mean serum albumin levels were recorded between patients undergoing hemodialysis for 6-10 years (86.91 ± 2.31 units, 71.62 ± 2.7 units and 2.50 ± 0.63 g/dL, respectively) and patients undergoing hemodialysis for 6 months to 5 years (67.78 ± 0.92 units, 53.05 ± 2.1 units and 3.70 ± 0.48 g/dL, respectively) (Table 4, Figures:2,3).

DEHP serum levels (Table5, Figure: 4)

Significant increases ($p<0.01$) were recorded in DEHP mean serum levels between the control group (0.68 ± 0.08 mg/ml), and pre- (1.69 ± 0.79 mg/ml) & post-dialysis blood samples (3.15 ± 0.89 mg/ml), of patients undergoing regular hemodialysis therapy from 6 months till 5 years.

A non-significant increase ($p>0.05$) was recorded between postdialysis blood samples (3.15 ± 0.89 mg/ml) and the predialysis blood samples (1.69 ± 0.79 mg/ml), of patients undergoing regular hemodialysis therapy from 6 months till 5 years (n=10).

Significant increase ($p<0.05$) were recorded in DEHP mean serum level between the control group (0.68 ± 0.08 mg/ml), and pre- (2.51 ± 0.81 mg/ml) & post-dialysis blood samples (4.23 ± 1.26 mg/ml), of patients undergoing

regular hemodialysis therapy from 6-10 years .

A significant increase ($p<0.05$) was recorded in DEHP mean serum level between postdialysis blood samples (4.23 ± 1.26 mg/ml) and predialysis blood samples (2.51 ± 0.81 mg/ml), of patients undergoing regular hemodialysis therapy for 6-10 years (n=10).

A significant increase ($p<0.01$) was recorded between DEHP mean serum level of the predialysis blood samples (2.51 ± 0.81 mg/ml) of patients undergoing regular hemodialysis therapy for 6-10 years (n=10) and predialysis blood samples (1.69 ± 0.79 mg/ml)of patients undergoing regular hemodialysis from 6 months till 5 years (n=10).

A significant increase ($p<0.05$) was recorded in DEHP mean serum level between postdialysis blood samples (4.23 ± 1.26 mg/ml) of patients undergoing regular hemodialysis therapy for 6-10 years (n=10) and postdialysis blood samples (3.15 ± 0.89 mg/ml) of patients undergoing regular hemodialysis therapy from 6 months till 5 years (n=10).

- Correlation Study

Positive significant correlation ($p<0.05$) was calculated between DEHP mean serum level of the predialysis blood samples (n=20) (2.10 ± 0.89 mg/ml) and the duration of hemodialysis therapy from 6 months till 10 years (r= 0.57*) (Figure: 5).

No correlation ($p>0.05$) was calculated between DEHP mean serum level of the predialysis blood samples (n=20) (2.10 ± 0.89 mg/ml) and the mean serum albumin level for patients undergoing hemodialysis therapy from 6 months till 5 years (3.7 ± 0.48 g/dL) and patients undergoing regular hemodialysis therapy for 6-10 years (2.5 ± 0.63 g/dL) (r= 1.08 and 0.69, respectively).

DISCUSSION

The present study provides quantitative data on the concentration of diehtylhexyl phthalate (DEHP) in the venous blood of 2 groups of subjects. The first group was for healthy volunteers not exposed to any of the DEHP containing medical devices.

Despite the absence of exposure of those healthy volunteers to any medical device till the time of the study, six of them had detectable DEHP serum levels. This was explained by Koch et al. (2003) who stated in their study that humans are exposed to DEHP through ingestion, inhalation, and dermal exposure for their whole lifetime, since the intrauterine life, with the predominance of the oral route exposure. Also, Heudorf et al. (2007)

suggested that due to the ubiquitous use of DEHP in numerous products and due to their ability to migrate into the various environmental compartments, DEHP can be detected not only in consumer products, but also in food and in the indoor environment resulting in contamination levels of indoor air and household dust.

Regarding the group of patients undergoing hemodialysis on regular basis, two crucial issues have been demonstrated. The first is that, dialysis patients are exposed continuously to DEHP during the dialysis sessions, and which is not cleared from their sera. This is represented by the elevated serum levels of DEHP prior to and after the dialysis. This can be explained by the work of Schmid and Schlatter (1985) who stated that DEHP and its hydrolysis products are rapidly eliminated by the kidney and in the faeces in healthy subjects, accordingly patients with impaired renal function and patients requiring dialysis treatment have an increased body burden of plasticizers, presumably for two reasons: firstly, as a result of the exposure to plastic materials during dialysis, and secondly, due to a decreased urinary elimination of these compounds. This is supported by Heudorf et al. (2007) who mentioned that DEHP is the most commonly used plasticizers in a wide variety of medical and technical products; consequently it can be incorporated in the human body and can be detected in the blood.

The second important issue provided by the present study is, a quantitative estimation for the exposure of hemodialysis patients to DEHP during the hemodialysis sessions. Faouzi et al. (1999) evaluated the exposure to DEHP for the general population and patients during medical procedures, and stated that long-term hemodialysis is the continuously repeated procedure, which may result in the highest cumulative dose of DEHP (up to 2.2 mg/kg/d) with a range of 20-360 ug/kg retained dose by the patients. Besides, Dine et al. (2000) recorded an average of 18 mg/ml DEHP retained in venous blood of patients undergoing a 3-hours dialysis session treatment, repeated three times per week, during several months, reached a conclusion that DEHP concentrations may reach a high level and the dialysis treatment may expose patients to DEHP effects when using PVC tubing over prolonged periods of time. The same conclusion was reached by Kambia et al. (2001) who found that the total amounts of DEHP retained in the patients' blood, on maintenance hemodialysis for 1-7 years, were 27.30$\pm$9.22 mg (ranging from 12.50 to 42.72 mg).

This continuous DEHP exposure may violate the non-maleficence principle of

bioethics. Non-maleficence is one of the 4 principles of medical bioethics and it refers to "do not harm others" (Lawson, 2010), and in the same time as Lawrence (2007) stated, beneficence and non-maleficence are the two sides of the same coin.

The compromise of the non-maleficence principle can be demonstrated in the significant changes detected in the liver functions of the hemodialysis patients of the present study. Cooper et al. (2008) stated that research has linked DEHP to a variety of hepatotoxic changes. David et al. (2001) detected a significant alteration in the liver functions (ALT, AST, bilirubin and albumin) measured in their experimental study. This later was explained by Rusyn et al. (2006) who stated that the industrial plasticizer DEHP belongs to a class of chemicals known as peroxisome proliferators (PPs) and that induction of cell proliferation, decreased apoptosis, oxidative DNA damage, and selective clonal expansion of the initiated cells have also been proposed to be critically involved in peroxisome proliferation-induced carcinogenesis in liver.

Regarding the serum albumin level, Iseki and co-workers (1997), conducted a prospective four-year study of 1243 chronic hemodialysis patients about the level correlation between serum albumin concentration and hemodialysis patient survival. It was concluded that patients, who began dialysis with serum albumin concentrations less than 3.5 gm/dl, had a five year survival of less than 50%, compared to a more than 80% five-year survival for patients with baseline serum albumin concentration of 4.5 gm/dl or greater, and that patients with baseline serum albumin concentration between 3.5 and 4 gm/dl had a five-year survival of approximately 70 percent.

Owing to the crucial findings of the present and referred studies, it's highly recommended to use DEHP-free medical devices, especially for patients undergoing regular hemodialysis who are considered of the highest risk population that are exposed continuously to DEHP hazards. This recommendation is supported by "The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)" (2008) who has evaluated the exposure to DEHP for the general population and patients during medical procedures, and found that, in some cases the exposure is significant and exceeds the toxic doses observed in animal studies, and it is recognized that especially the potentially high exposure during medical treatments may raise a concern, even in the absence of clinical or epidemiological evidence, for harmful effects in humans.

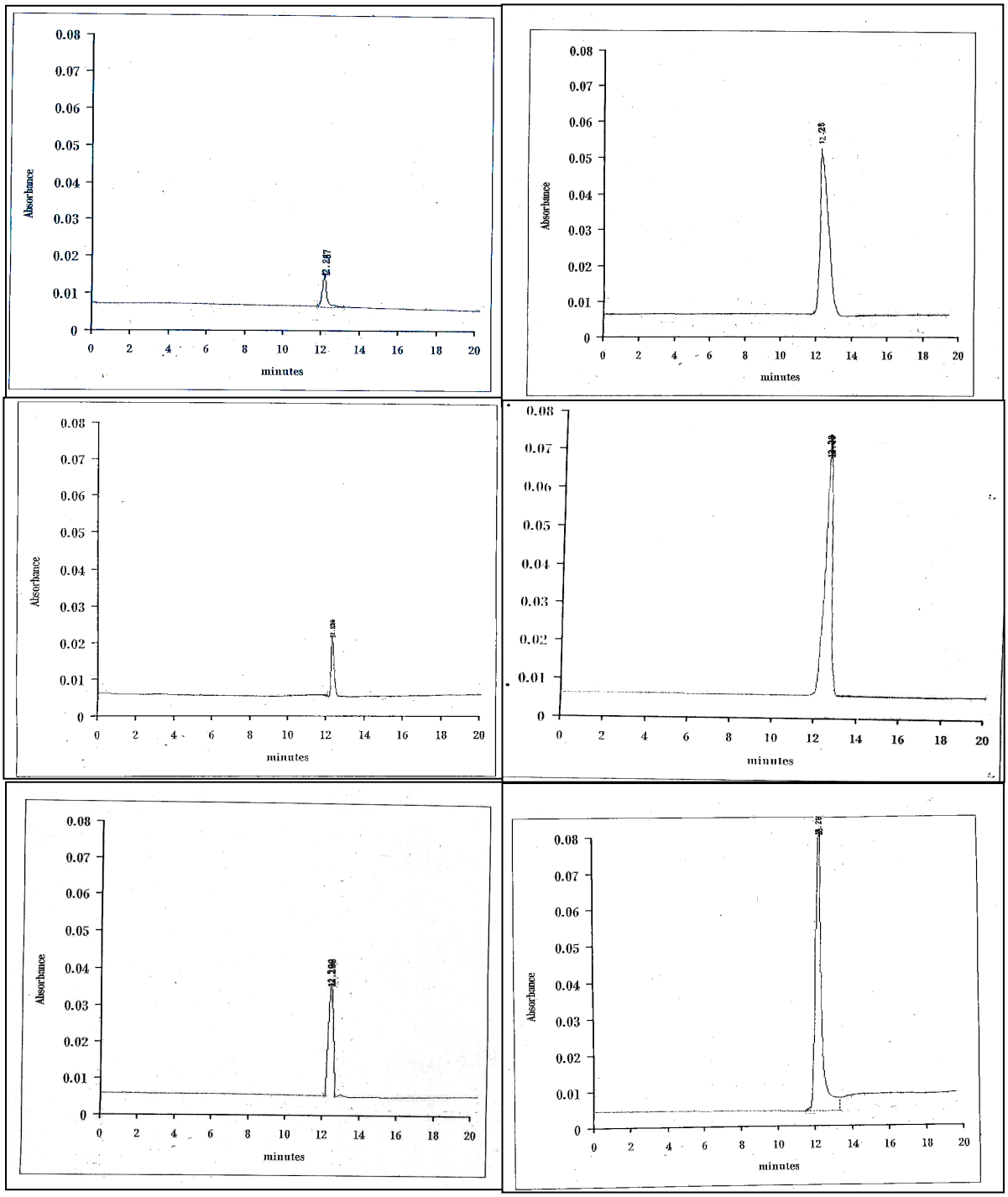


Figure (1): Shows chromatogram of DEHP (a) 0.05µg/ml, (b)0.1µg/ml, (c) 0.5µg/ml, (d) 2.5µg/ml, (e) 4.5µg/ml, (f) 5.0µg/ml, standard concentration, detected by UV detector at wavelength 270 nm.

able (1): Demographic characters of the studied subjects .

	Female (N^o)	Male (N^o)	Age (Years)
Control	6	4	35-50
HD 6 months-5 years	5	5	30-55
HD 6-10 year s	3	7	45-70

HD: hemodialysis

Table (2): Shows liver function tests of the control group and patients undergoing hemodialysis (HD) from 6 months - 5 years.

Liver Functions	Control	HD patients (6 months to 5 years)	*p*-value
ALT (units)	29.45 ± 2.10	67.78 ± 0.92	$p<0.01$*
AST (units)	15.04 ± 1.70	53.05 ± 2.1	$p<0.01$*
Albumin (g/dL)	6.80 ± 1.73	3.70 ± 0.48	$p<0.01$*

*P is significant at<0.05.

Table (3): Shows liver function tests of the control group and patients undergoing hemodialysis (HD) from 6 - 10 years.

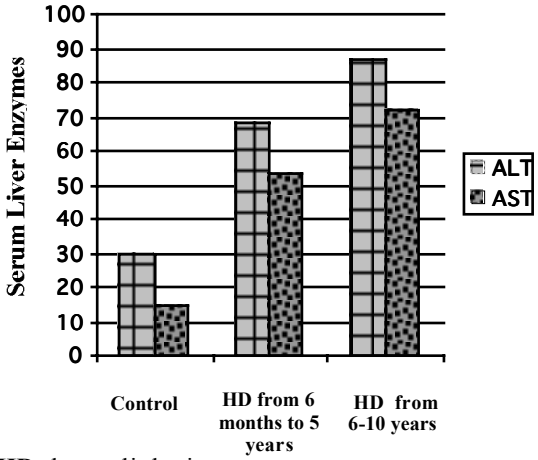
Liver Functions	Control	HD patients (6 -10 years)	*p*-value
ALT (units)	29.45 ± 2.10	86.91 ± 2.31	$p<0.001$*
AST (units)	15.04 ± 1.70	71.62 ± 2.7	$p<0.001$*
Albumin (g/dL)	6.80 ± 1.73	2.50 ± 0.63	$p<0.001$*

*P is significant at<0.05.

Table (4): Comparison of liver function tests of the patients undergoing hemodialysis (HD) from 6 months to 5 years and 6 - 10 years.

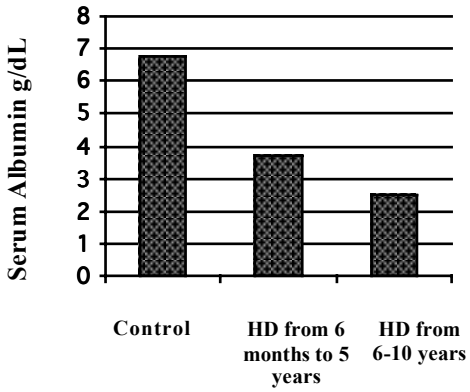
Liver Functions	HD patients (6 months to 5 years)	HD patients (6 -10 years)	*p*-value
ALT (units)	67.78 ± 0.92	86.91 ± 2.31	$p<0.05$*
AST (units)	53.05 ± 2.1	71.62 ± 2.70	$p<0.05$*
Albumin (g/dL)	3.70 ± 0.48	2.50 ± 0.63	$p<0.05$*

*P is significant at<0.05.



HD: hemodialysis

igure (2): Shows liver enzymes concentration in the 3 studied groups.



HD: hemodialysis

Figure (3): Shows mean albumin serum level for the 3 studied groups.

Table(5): Shows serum DEHP concentration of the control group, pre- and post-dialysis blood samples of the studied groups undergoing hemodialysis for 6 months- 10 years.

	Control Group*	HD duration from 6 months-5 years		HD duration from 6-10 years	
		Predialysis	Postdialysis	Predialysis	Postdialysis
Serum DEHP Concentration	0.68 + 0.08	1.69 ± 0.79[a],	3.15 ± 0.89[a,b],	2.51 ± 0.81[a],	4.23 ± 1.26[a,b],

HD Hemodialysis
a Significant increase over control group at $p \leq 0.05$
b Significant increase over predialysis group at $p \leq 0.05$
c Significant increase over predialysis group of HD duration 6 months-5 years at $p \leq 0.01$
d Significant increase over postdialysis group of HD duration 6 months-5 years at $p \leq 0.05$

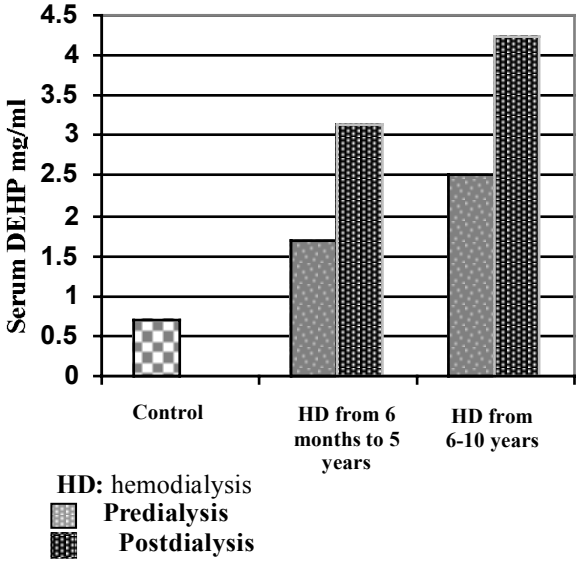
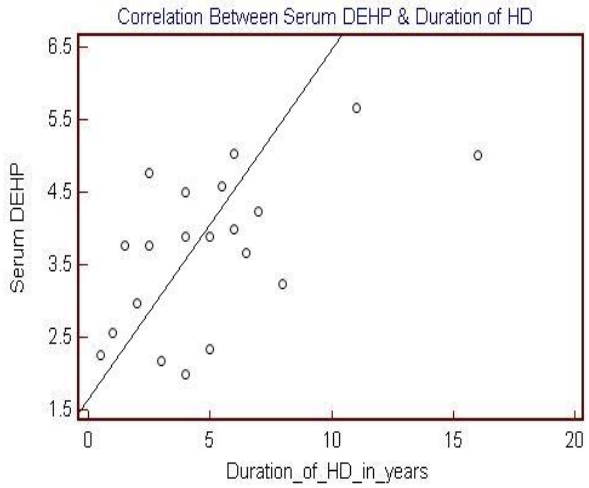


Figure (4): Shows DEHP serum concentration between the control group, pre- and post-dialysis blood samples for patients undergoing hemodialysis from 6 months to 5 years, and 6-10 years.



HD: hemodialysis

Figure (5): Shows correlation between serum DEHP and the duration of hemodialysis.

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معضلة أخلاقية جديدة يتعرض لها مرضى الغسيل الكلوى : التعرض لثنائى الإثيل هكسايل ثاليت

المشتركون فى البحث

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يتعرض المرضى الذين يخضعون لغسيل الكلى إلى أجهزة طبية تحتوى على ثنائى الإثيل هكسايل ثاليت أثناء إجراء الغسيل الكلوى، وبسبب الاستخدام الواسع النطاق لثنائى الإثيل هكسايل ثاليت بالأجهزة الطبية وفى الحياة، يعد هذا العمل خطوة ضرورية للتحديد الدقيق لمدى تعرض المرضى الذين يخضعون للغسيل الكلوى بصورة منتظمة من أجل تقييم المخاطر من الإثيل هكسايل ثاليت على كبد الإنسان.

تم قياس مستوى ثنائى الإثيل هكسايل ثاليت ومستوى إنزيمات الكبد والزلال فى 30 شخصاً ، حيث كان 10 منهم متطوعين أصحاء كمجموعة ضابطة والباقى من مرضى الغسيل الكلوى، المجموعة الأولى منهم تمثل فترة الغسيل الكلوى من 6 أشهر إلى 5 سنوات، والمجموعة الثانية تمثل فترة الغسيل الكلوى من 6 إلى عشرة سنوات، ووجد إرتفاع ذو دلالة إحصائية فى مستوى الإثيل هكسايل ثاليت وأيضاً تغيرات ذات دلالة إحصائية بوظائف الكبد، بين المجموعة الضابطة ونتائج مرضى الغسيل الكلوى.

مماسبق، يتضح أن التعرض المستمر لمرضى الغسيل الكلوى لمادة ثنائى الإثيل هكسايل ثاليت قد يحدث آثاراً سمية على كبد الإنسان وهذا يتعارض مع مبادىء أخلاقيات مهنة الطب ألا وهى عدم الإضرار، ولهذا ينبغى الإقلال من إستخدام الأجهزة الطبية التى تحتوى أجزاؤها على مادة ثنائى الإثيل هكسايل ثاليت.