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Research Article

# A Cross-Sectional Survey of Estimated Glomerular Filtration Rate, Acid-Base Balance and Electrolyte Status among Workers Exposed to Petroleum Products

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## Abstract

**Aim:** To investigate the effect of exposure to petroleum products on eGFR, acid-base balance and electrolyte homeostasis among gasoline station workers in Uyo, Southeastern Nigeria.

**Methods:** A cross-sectional study was performed on 68 (38 exposed and 30 unexposed) gasoline station workers who met the inclusion criteria. The instruments of survey included a semi-structured questionnaire, anthropometric measures and biochemical markers of renal function and hematological indices assessment. Values in the exposed group were compared to the corresponding values in the unexposed group.

**Results:** Serum anion gap, Cr, Ur, $K^+$ and urinary excretion of electrolytes ($Na^+$ and $K^+$) and urea increased significantly ($p<0.01$), while eGFR, $Cl^-$ and pH levels decreased significantly in the exposed subjects compared to the corresponding level in the unexposed subjects.

Urinary Cr and $HCO_3^-$ significantly decreased in male and female subjects respectively, but the decrease in pH did not reach statistical significance, while urinary $K^+$ and UAG significantly increased only in exposed female subjects. Red blood cell indices (PCV, HB, MCH, MCHC, MCV and total RBC) and EOS counts significantly decreased and increased in male and female subjects, respectively.

**Conclusion:** Long-term exposure to petroleum products may be associated with significant decrease in eGFR, normal serum AG, positive urinary AG, azotemia and urinary excretion of electrolytes and hematotoxicity. Intervention programs to limit exposure and /or protect exposed workers against the potential detrimental effects of petroleum compounds on renal endpoints across different petro-chemical industries are strongly recommended.

## Introduction

Incidence of kidney diseases leading to kidney failure is increasing [1]. Kidney failure is a growing burden in terms of quality of life, morbidity, mortality and economy. Many factors contribute to the development of kidney disease worldwide including occupational exposure to solvents such as gasoline [2-7]. Gasoline (petrol) is a fractionated product of crude petroleum and has a mixture of over 500 saturated and unsaturated hydrocarbons [8] that typically contain between 3-12 carbons per molecule [9]. It is a complex, volatile and flammable liquid used extensively as fuel for automobiles and as industrial solvent, pesticide and cleansing agent [10].

Evidence accumulated has shown that people can be occupationally exposed to toxic gasoline constituents with resultant adverse health outcomes. Petroleum products retailing is an example of an occupation that exposes its workers to having a direct contact with significant quantity of gasoline constituents per unit time through inhalation, dermal or accidental ingestion. However, inhalation route poses a more serious public health hazard due to the high accessibility and excellent absorption surface of the respiratory tract that makes the constituent hydrocarbons readily absorbed by the lungs [11,12].

One study [13] showed that service station workers are exposed to gasoline inhalation many hours a week, approximately 8086 minutes per year. Besides gasoline station workers, many others are exposed to gasoline constituents during its procurement for domestic or commercial uses [14]. The frequency and amount of use of gasoline creates many potential exposures in a typical day. According to Wixton and Brown [15], about 110 million people are exposed to gasoline constituents within a few minutes per week and about 100 min/year during refueling at self- service gasoline station [9]. In terms of country ranking, United State of America tops the list of the first 10 countries regarded as the high- volume consumer of petroleum products [16], followed by Canada, Kuwait, Luxemboug, Saudi Arabia, Oman, Brunei, Qatar, Australia and New Zealand.

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In Nigeria, more than 10% of the population is continuously exposed to gasoline with associated systemic adverse health effects [17]. When inhaled, vapors absorbed by the lungs are transported to the blood stream, and distributed to other organs including the kidney [2]. Human kidney receives about 20% of a cardiac output, with the largest renal blood flow (90%) perfusing the renal cortex, while the medullary zone receives approximately 10% of the renal blood supply [18].

Despite the extensive used and prolonged exposure to petroleum products, and the speculated renotoxic effects, there are no empirical data on the effect of gasoline exposure on some surrogate markers of renal endpoints including Estimated Glomerular Filtration Rate (eGFR), acid-base balance and renal handling of electrolytes and solutes. Some studies have reported significant association between exposure to gasoline and changes in serum electrolyte, urea and Creatinine (Cr) levels.

Whereas, others have found non-significant effect between exposure and serum levels of these substances, thereby making the postulated nephro-toxic effect of gasoline constituents a controversial scientific issue [19,20].

Besides these inconsistent/conflicting research findings, most of these studies made use of serum or urinary levels of these substances alone to assess the functional status of the kidney among exposed workers. This may not reflect the actual degree of renal function in some patients due to the effect of several confounding variables on serum, or urinary level of these substances including age, sex and body mass. Furthermore, most of these studies were animal based, making the results not completely applicable to humans due to the unique metabolism and distribution of some gasoline constituents (e.g., benzene) in humans, leading to increased susceptibility to the toxic effect of these constituents.

Given the drawbacks of previous studies, the present study was aimed at assessing the effect of chronic exposure to gasoline on eGFR, anion gap and urinary excretion of electrolytes and solutes among exposed gasoline station workers, which hitherto has not been studied.

Estimation of GFR using predictive formulas provides the best index of renal function assessment for diagnostic and therapeutic reasons [21]. It is of central importance in determining the degree of renal function impairment. Serum anion gap is use in the detection and analysis of acid-base disorders [22], while urinary excretion of electrolytes provides reliable index of renal handling of electrolytes and water. It relates the amount of electrolyte excreted to the amount filtered [23].

## Methods

### Selection of subjects

The study was a multi-site cross-sectional survey on the adverse health effect of Gasoline Vapor (GV) on the exposed gasoline station workers within Uyo metropolis. Sixty-eight gasoline station workers of the 89 workers invited to participate in the survey met the inclusion criteria and were assessed for changes in serum and urinary biomarkers of renal function. The exclusion criteria were as follows; History of kidney or liver disease, inappropriate age (< 18 and > 35 years), declined participation, missing information, improper completion of questionnaire, those who have worked for < 1 year at the time of the survey and evidence of any metabolic syndrome clusters e.g., diabetes mellitus, hypertension, obesity and dyslipidemia. Those on medications for any of these metabolic disorders or medications known to affect renal function such as diuretics, non-steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors were also excluded. Also excluded from the study were smokers, alcohol and caffeine users. All participants who met the inclusion criteria provided an informed written consent to participate, and Institutional Ethic Committee approved the study protocol.

The study was conducted in line with the guidelines set forth in the 1964 declaration of Helsinki governing the conduct of human research.

### Survey methods

**Instruments of survey:** Three survey instruments were used to survey the participants who had worked for at least 1 year as gasoline station operators. These included; a semi structured questionnaire adapted from previous studies [24] conducted among gasoline station workers. The questionnaire was divided into 2 sections (section 1 and 2). Section 1 contained information on the socio-demographic characteristics of the participants including age, sex, lifestyle habits, while section 2 consisted of questions aimed at obtaining information about participants past and present renal, cardiovascular and hematologic profiles.

### Measurements

**Anthropometric indices:** Anthropometric indices of participants measured were weight and height.

**Measurement of weight:** Weight was measured in kilogram to the nearest 0.1kg using weighing scale (Seca Model, Germany). Prior to the measurement, participants were instructed to wear light clothing and without shoes. To maintain accuracy, the scale was adjusted to zero after each weighing prior to the next measurement and weighing was performed twice and average reading was used for statistical analysis. Errors due to parallax were minimized by placing the scale on a flat but solid surface and the reading taken vertically.

**Measurement of height:** The height was measured by making the subjects to stand erect against the graduated and adjustable height measuring metallic scale attached to the weighing scale. A ruler was placed on the subjects head to get the exact point on the scale. Accuracy was ensured by taking the reading without shoes and standing erect against the wall, looking straight ahead while the height was taken to the nearest 1 cm and both feet were placed closed together on a level ground.

Body mass index (BMI-Quetelets index) was calculated from the formula BMI = weight (kg)/Height ($m^2$).

### Biochemical Estimation

Twelve-hour urine sample was collected from all participants in their respective 4 liter sterile plastic containers between the hours of 7pm and 7am. The Urine Volume (UV) was measured with a calibrated cylinder. Participants were instructed to ensure accuracy in the collection of the urine sample. An aliquot of 10 ml urine was pipetted into a plain sterile bottle and centrifuged at 300 rpm at room temperature for 15 minutes.

The supernatant was diluted with a urine diluent (1:2 ratio), and samples were used for chemical analysis including urinary sodium ($Na^+$), potassium ($K^+$), chloride (Cl) and calcium ($Ca^{2+}$) using ion-selective electrolyte analyzer (Biolyte 200-Biocare corporation, Hsinchu 3000, Taiwan).

Urine and plasma pH were determined with a digital pH meter (Model E9610 Equiptronic, England). Fasting venous blood samples obtained from participants were used for analysis for some biochemical indices of renal function including urea (Ur), creatinine (Cr), hydrogen concentration (pH) and electrolytes $Na^+$, $K^+$, $Cl^-$ and $HCO_3^-$.

Serum electrolytes ($Na^+$ and $K^+$) levels were determined using a flame photometer, while serum and urinary Cr levels were determined according to Jaffe kinetic method (Sigma Chemical Co. USA). Three test tubes containing standard, serum and blank, respectively were set up. The serum and standard were deproteinized with equal amount of tungstic acid. One milliliter of distilled water was added to all the test tubes after which 1 ml of Sodium Hydroxide (NaOH) and picric acid were added to the tubes. After 5 minutes, spectrophotometric reading was taken at 520 nM and the concentration of serum Cr was calculated using standard formulas.

For urine specimens, the absorbance concentration obtained was multiplied by 10.

Serum and urinary bicarbonate ($HCO_3$) levels were determined by enzymatic method. Serum Urea (Ur) and Uric Acid (UA) were measured using a multichannel automated analyzer (SYNCHRON, Los Angeles, CA, USA). Urinary glucose and protein were measured by means of dipstick reagent strip (Medi-Test Combi 9-Germany).

The use of 12 h urine samples in the present study is in line with previous studies [20] that confirmed the reliability of 12 h urine samples in estimating 24 h intake/excretion of electrolytes in clinical settings [25].

Quality control measures to ensure accuracy included disqualification of urine or blood samples not properly collected, repeated analysis of stock urine or blood samples with extremes of values, using an average of two measurements for statistical analysis and cleaning and conditioning of instruments (Digital ion-selective electrolyte analyzer and pH meter) with standard commercially prepared regents every time after use.

### Assessment of renal function

**Creatinine clearance estimation using predictive formulas:** Estimated Glomerular Filtration Rate (eGFR)/ Serum Creatinine Clearance Rate (SCrcl) was estimated using Cockcroft Gault (G-C) formula [26].

SCrcl (mL/minute) = (140-age [years]) × Weight (kg) × 0.85 (if female)/72 × Scr (mg/dL).

This was normalized per 1.73 $m^2$ of Body Surface Area (BSA) using the formula of DuBois and DuBois [27]. This was to enable comparison with the prediction of other formulas. Also, eGFR was calculated using Modification of Diet in Renal Disease (MDRD) equation [28] represented as;

eGFR (ML/min/1.73$m^2$)= 175 (SCr (mmol/L))$^{-1.154}$ × [Age (years)]$^{-0.203}$ × 1.212 (if black) × (0.742 (if female).

### Estimation of acid-base status of participants (Anion gap)

**Serum Anion Gap (SAG) estimation:** Serum anion gap is the difference between primary measured cations ($Na^+$ and $K^+$) and primary measured anions ($Cl^-$ and $HCO_3^-$) in serum.

SAG was estimated using the equation = ($Na^+$ + $K^+$) - ($Cl^-$ + $HCO_3^-$)

Urine anion gap (UAG) was estimated using the formula

$U_{AG}$ = ($Na^+$ + $K^+$) - ($Cl^-$)

Normal value suggests adequate excretion of $NH_4^+$ ($Cl^-$ > $Na^+$ + $K^+$).

Conversely, a positive value of 0 to + 50 indicates a defect in $NH_4^+$ excretion.

The hematologic parameters measured included Packed Cell Volume (PCV), Haemoglobin (HB), concentration, total Red Blood Cell (RBC) count, Mean Cell HB (MCH), Mean Cell HB Concentration (MCHC), Mean Cell Volume (MCV) and White Blood Cell (WBC) -total and differentials and platelet counts. The measurements were performed within 2 h of sample collection using the SYSMEX Kx-21 Automated Hematology Analyzer (Kobe, Japan).

## Statistical Analyses

Data obtained were analyzed comparatively using frequencies, percentages, means, standard deviation and independent t-test. Frequencies and percentages were used to analyze categorical variables while quantitative variables were analyzed using means and standard deviation. Also, independent t-test was used to compare differences in serum and urinary electrolytes, red blood cell indices and white blood cell indices between the exposed and unexposed subjects.

Association between categorical variables were examined using chi-square and statistical significance was established at 5% with $p<0.05$. Data were analyzed using graphed prism 5.0 and Statistical Package for Social Sciences (SPSS version 20.0).

## Results

This multi-site cross-sectional survey included 68 participants (38 exposed and 30 unexposed) selected from 89 subjects who were initially invited to participate in the survey, representing a response rate of 76.4%. From the data obtained, it was observed that the socio-demographic variables were not significantly different between the exposed and unexposed participants (Table 1).

Changes in serum biochemical indices of renal function in the exposed subjects significantly differed from the unexposed subjects in Cr, Urea, pH, $Cl^-$, $Na^+$, $K^+$ and MDA. Specifically, serum Cr, Ur, K and MDA significantly increased in the exposed group when compared to their corresponding values in the unexposed group. Serum $Cl^-$ significantly ($p<0.05$) decreased in the exposed male and female subjects when compared to the value in the unexposed male and female subjects. Serum $Na^+$ and $HCO_3^-$ showed no significant change in female subjects, whereas a significant and a non-significant increase in serum $Na^+$ and $HCO_3^-$ levels respectively, were observed in male subjects. Hydrogen ion concentration increased (decreased pH) in the exposed subjects when compared to the corresponding level in

**Table 1:** Demographic characteristics of exposed and unexposed participants.

| Demographic Variables | Total (n=68) | Exposed (n=38) | Unexposed (n=30) | *p*-value |
|---|---|---|---|---|
| Age (Mean ± SD) | 27.00 ± 3.75 | 28 ± 3.44 | 26 ± 3.01 | 0.0144 |
| **Sex** | | | | |
| Male | 41 (60.3) | 22 (57.9%) | 19 (63.3%) | 0.837 |
| Female | 27 (39.7) | 16 (42.1%) | 11 (36.7%) | |
| Weight (kg) | 61.45 ± 6.42 | 62 ± 4.22 | 60.9 ±3.84 | 0.6821 |
| Height (m) | 1.52 ± 0.48 | 1.5 ± 0.42 | 1.54 ± 0.21 | 0.6355 |
| BMI (Mean ± SD) | 26.62 ± 5.76 | 27.55 ± 5.22 | 25.68 ± 2.53 | 0.0764 |
| **Marital Status** | | | | |
| Single | 55 (80.9) | 29 (76.3%) | 26 (86.7%) | 0.443 |
| Married | 13 (19.1) | 9 (23.7%) | 4 (13.3%) | |
| **Educational status** | | | | |
| Secondary | 45 (66.2) | 26 (68.4%) | 19 (63.3%) | 0.559 |
| OND/NCE | 22 (32.4) | 11 (28.9%) | 11 (36.7%) | |
| HND/BS.c | 1 (1.5) | 1 (2.6%) | 0 (0.0%) | |
| **Physical activity status** | | | | |
| Active | | | | 0.523 |
| Inactive | 29 (42.6) | 18 (47.4%) | 11 (36.7%) | |
| | 39 (57.4) | 20 (52.6%) | 19 (63.3%) | |
| **Ethnicity** | | | | |
| Ibibio | 40 (58.8) | 19 (50.0%) | 21 (70.0%) | 0.319 |
| Annang | 18 (26.5) | 12 (31.6%) | 6 (20.0%) | |
| Igbo | 7 (10.3) | 5 (13.1%) | 2 (6.7%) | |
| Others | 3 (4.4) | 2 (5.3%) | 1(3.3) | |

the unexposed male and female subjects, but only the increase in male subjects reached statistically significant level (Table 2).

Table 3 shows that some urinary biochemical indices in the exposed group significantly differ from the corresponding values in the unexposed group including Cr level which significantly decreased in exposed male and female subjects, and $HCO_3^-$ concentration which significantly decreased in exposed females compared to the levels in the unexposed females.

Urinary $K^+$ significantly increased in the exposed male and female subjects compared to the corresponding values in the unexposed male and female subjects. Also, there were non-significant increases and decreases in urinary $Na^+$ and Ur levels respectively, in both exposed male and female subjects. The results obtained also show that PCV, HB and other red blood cell indices (MCH, MCHC, MCV and RBC) were significantly higher in the unexposed than exposed male and female subjects (Table 4).

**Table 2:** Effect of gasoline exposure on serum electrolytes and acid-base balance of exposed workers.

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| **Parameters** | **Exposed** | **Unexposed** | ***p*-value** | **Exposed** | **Unexposed** | ***p*-value** |
| Creatinine (mg/dl) | 94.01±0.35 | 79.04 ± 0.20 | 0.004* | 92.03 ± 0.26 | 72.06 ± 0.15 | 0.0004** |
| Urea (mg/dl) | 27.29±7.88 | 17.50 ± 2.91 | 0.0001** | 26.68 ± 6.69 | 16.70 ± 2.26 | 0.0001** |
| Ph | 7.36 ± 0.17 | 7.38 ± 0.06 | 0.0001** | 7.34± 1.10 | 7.39± 0.18 | 0.3533 |
| $HCO_3$ (mEq/L) | 25.43 ± 1.87 | 25.20 ± 1.55 | 0.5895 | 24.37 ± 2.29 | 25.30 ± 1.89 | 0.0775 |
| Chloride(mEq/L) | 99.57 ± 3.23 | 105.40 ± 10.55 | 0.0020** | 100.37 ± 5.13 | 103.30 ± 4.14 | 0.0134* |
| Na (mEq/L) | 136.71 ± 7.14 | 132.30 ± 3.13 | 0.0025** | 134.79 ± 6.13 | 133.30 ± 4.14 | 0.2581 |
| K (mEq/L) | 4.01 ± 0.56 | 3.59 ± 0.30 | 0.0004** | 4.04 ± 0.67 | 3.65 ± 0.30 | 0.0043** |
| Glucose(mg/dl) | 91.93 ± 15.50 | 86.80 ± 8.30 | 0.1067 | 75.47 ± 18.25 | 85.90 ± 9.97 | 0.0065* |
| MDA(ng/ml) | 98.78 ± 5.88 | 96.00 ± 2.26 | 0.0170* | 98.53 ± 4.98 | 94.70 ± 1.49 | 0.0001** |

*** = significantly at 5% (*p*<0.05),**

** = significant at 1% (*p*<0.01).

**Citation:** Ekpenyong CE and Inyang MAE. A Cross-Sectional Survey of Estimated Glomerular Filtration Rate, Acid-Base Balance and Electrolyte Status among Workers Exposed to Petroleum Products. J Nephrol Kidney Dis. 2017; 1(2): 1008.
https://dx.doi.org/10.36876/smjnkd.1008

**Table 3:** Effect of gasoline exposure on urine electrolytes and acid-base homeostasis of exposed and unexposed workers.

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| **Parameters** | **Exposed** | **Unexposed** | ***p*-value** | **Exposed** | **Unexposed** | ***p*-value** |
| Creatine (mg/dl) | 581.30 ± 0.16 | 840.50 ± 0.32 | 0.0001** | 701.20 ± 0.19 | 710.30 ± 0.29 | 0.8709 |
| Urea (mg/dl) | 21.70 ± 2.58 | 24.63 ± 9.47 | 0.108 | 22.00 ± 2.11 | 24.27 ± 8.10 | 0.1401 |
| PH | 6.11 ± 0.34 | 7.22 ± 0.12 | 0.096 | 6.08 ± 0.21 | 7.14 ± 0.06 | 0.1346 |
| $HCO_3$ (mEq/L) | 23.75 ± 2.87 | 23.50 ± 1.58 | 0.6575 | 22.00 ± 2.33 | 23.30 ± 1.34 | 0.0084** |
| Chloride (mEq/L) | 96.88 ± 5.59 | 98.88 ± 2.95 | 0.0809 | 101.53 ± 6.40 | 103.10 ± 1.20 | 0.1903 |
| Na (mEq/L) | 134.25 ± 3.11 | 132.70 ± 3.27 | 0.0502 | 133.53 ± 9.30 | 132.30 ± 2.21 | 0.4816 |
| K (mEq/L) | 39.80 ± 0.66 | 36.20 ± 0.24 | 0.0060** | 43.30 ± 0.78 | 37.60 ± 0.31 | 0.0004** |

*** = significantly at 5% (*p*<0.05),**

** = significant at 1% (*p*<0.01).

**Table 4:** Effect of gasoline exposure on red blood cell indices in exposed and unexposed participants.

| **RBC** | **Male** | | | **Female** | | |
|---|---|---|---|---|---|---|
| **Indices** | **Exposed** | **Unexposed** | ***p*-value** | **Exposed** | **Unexposed** | ***p*-value** |
| PCV (%) | 33.65 ± 2.85 | 42.80 ± 3.29 | 0.0001** | 32.31 ± 4.38 | 44.10 ± 3.900 | 0.0001** |
| Hb (g/dL) | 13.06 ± 1.39 | 16.89 ± 8.48 | 0.078 | 12.91 ± 1.49 | 14.05 ± 0.96 | 0.0005** |
| MCH (pg) | 27.47 ± 2.60 | 30.70 ± 3.43 | 0.0001** | 27.13 ± 1.93 | 30.30 ± 2.58 | 0.0001** |
| MCHC (g/dl) | 29.47 ± 5.47 | 33.20 ± 1.75 | 0.0006** | 28.75 ± 5.11 | 33.20 ± 2.30 | 0.0001** |
| MCV (fL) | 63.08 ± 5.03 | 84.20 ± 3.39 | 0.0001** | 70.13 ± 13.73 | 82.70 ± 3.40 | 0.0001** |
| RBC (x106/µL) | 4.27 ± 0.98 | 4.90 ± 0.57 | 0.0026** | 4.06 ± 1.21 | 4.85 ± 0.47 | 0.0012** |

*** = significant at 0.05(*p*<0.05),**

** = significant at 0.01(*p*<0.01).

**Table 5:** Effect of gasoline exposure on white blood cell indices in exposed and unexposed participants.

| **WBC** | **Male** | | | **Female** | | |
|---|---|---|---|---|---|---|
| **Indices** | **Exposed** | **Unexposed** | ***p*-value** | **Exposed** | **Unexposed** | ***p*-value** |
| WBC (x$10^3$/µL) | 5.85 ± 2.77 | 5.20 ± 0.86 | 0.2203 | 6.69 ± 1.88 | 6.36 ± 1.60 | 0.446 |
| LYM (%) | 31.59 ± 2.87 | 38.40 ± 4.45 | 0.0001** | 32.81 ± 4.71 | 34.80 ± 4.59 | 0.0849 |
| MON (%) | 3.47 ± 1.50 | 3.50 ± 1.35 | 0.9321 | 3.75 ± 0.93 | 2.90 ± 0.86 | 0.0003** |
| BAS (%) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0 |
| EOS (%) | 7.71 ± 1.05 | 2.40 ± 1.07 | 0.0001** | 8.19 ± 0.91 | 2.20 ± 0.14 | 0.0001** |
| NEU (%) | 51.29 ± 5.14 | 52.50 ± 3.81 | 0.2857 | 52.88 ± 3.46 | 54.30 ± 3.50 | 0.0993 |

* = significant at 5% (*p*<0.05),

** = significant at 1% (*p*<0.01).

Changes in total WBC counts and WBC lineage counts include non-significant increase and decrease in total WBC counts and NEU counts respectively, in exposed versus unexposed male and female subjects. EOS counts increased significantly in both male and female subjects. LYM counts decreased in both male and female subjects but only the decrease in male subjects reached statistical significance. MONO counts decreased in exposed male, but significantly increased in exposed female subjects (Table 5).

Estimated GFR decreased significantly (p>0.05) in exposed male and female subjects using MDRD equation (Figure 1A) and C-G formula (Figure 1B). Serum Anion Gap (SAG) significantly increased (p<0.05) in exposed male and female subjects compared to the corresponding values in the unexposed groups (Figure 2). Also, urinary AG increased in exposed male and female subjects but the increase in male subjects did not reach a level of statistical significance (p<0.05) (Figure 3).

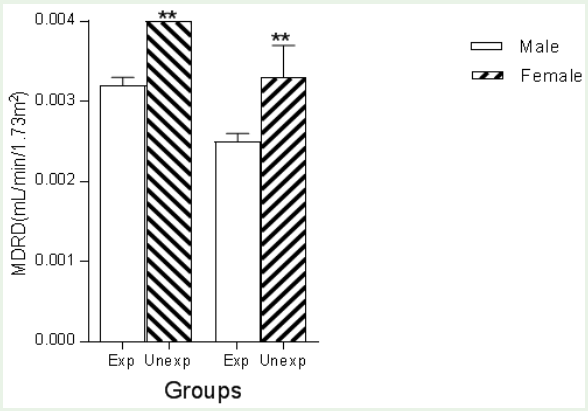


**Figure 1A:** Effect of gasoline exposure on estimated Glomerular Filtration Rate (eGFR) calculation using Modification of Diet in Renal Disease (MDRD) (mL/min/1.73m).
** = significant at 0.05(p< 0.05)

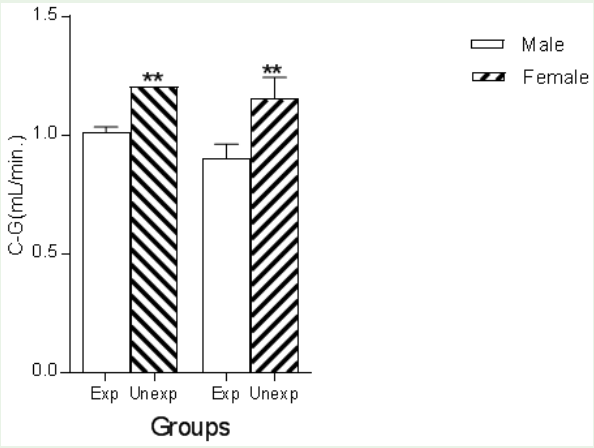


**Figure 1B:** Effect of gasoline exposure on Estimated Glomerular Filtration Rate (eGFR) calculation using Cockcroft-Gault (C-G) formula (mL/min).
** = significant at 0.05(p<0.05)

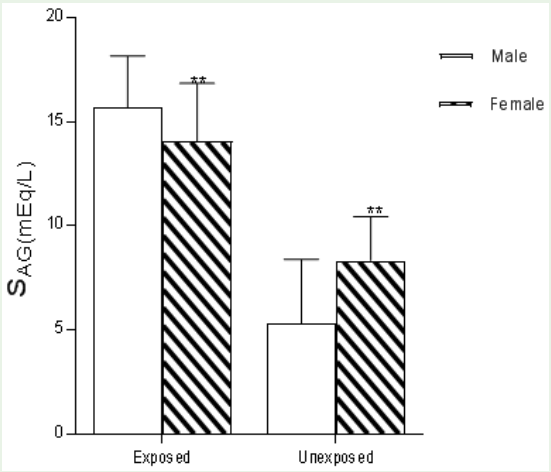


**Figure 2:** Effect of gasoline exposure on Serum Anion Gap ($S_{AG}$).
** = significant at 0.05 (p<0.05)

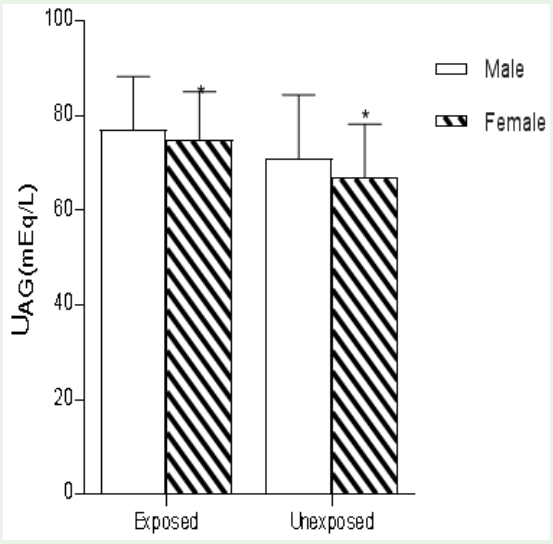


**Figure 3:** Effect of gasoline exposure on Urine Anion Gap ($U_{AG}$).
* = significant at 5% (p<0.05)

## Discussion

Results of this study show that long-term exposure to gasoline compounds is a significant risk factor for renal function impairment. This notion is supported by the statistically significant decrease in eGFR, alteration in acid-base balance and excretion of electrolytes leading to disturbances in serum electrolyte levels in exposed subjects compared to the levels in the unexposed subjects.

A significant decrease in eGFR suggests renal function impairment, and in particular, impairment in its ability to excrete/regulate the waste products of metabolism (e.g., Cr, Ur, UA and BUN); and maintain electrolytes and acid-base balance as observed in the exposed versus unexposed group. Interestingly, these changes in serum biochemical markers of renal endpoints also translated to changes in urinary physiochemical characteristics including positive urinary AG, significant changes in urinary Cr, Ur and K levels in the exposed subjects compared to the corresponding levels in control subjects.

The findings of decreased eGFR, normal serum AG, positive urinary AG, azotemia, decreased serum and urinary pH in the exposed subjects compared to the corresponding values in unexposed subjects suggest normal anion gap metabolic acidosis which suggests impaired renal excretory function, and in particular impairment in excretion of ammonium ions [29].

Collectively, the present study findings are consistent with those found in literature that suggested significant association between exposure to gasoline compounds and renal diseases [30-47]. At variance with the results of the present and previous studies, other studies [48,49] failed to demonstrate/justify a significant association between exposure to some gasoline compounds (toluene, xylene and styrene) and renal function impairment. This could probably be due to the confounding effects of several covariates including methodology issues (e.g., variation in study design [46,47], genetic susceptibility, age, duration of exposure, sex differences, composition and concentration of exposed hydrocarbons [50]).

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https://dx.doi.org/10.36876/smjnkd.1008

A number of mechanisms have been implicated in the pathogenesis of gasoline-induced renal function impairment including induction of Oxidative Stress (OS) [51,52], immune system dysfunction [53] and inflammation.

Following exposure, gasoline is bio-transformed into reactive metabolites which can directly impair renal function by binding covalently to renal macromolecules and leading to altered structure and biochemical function including impaired activities of some enzymes involved in homeostatic mechanisms (e.g., inhibition of sodium-potassium Adenosine Triphosphatase ($Na^+/K^+$/ATPase) activities. This enzyme system is responsible for the reabsorption of electrolytes ($Na^+$, $K^+$ and $Cl^-$), H+ and water in the renal tubules. Evidently, inhibition of this system could lead to disturbances in electrolytes, water and acid-base homeostasis as observed in the present and previous studies [52]. This could provide a logical explanation for the significant increase in serum Na and K levels, anion gap and urine anion gap; and decreases in serum pH and Cl levels in the exposed compared to the corresponding values in the unexposed group.

Interestingly, it was observed that the decreases in serum and urinary pH levels did not cause any significant alteration in serum $HCO_3$ levels. However, urinary $HCO_3$ levels decreased in both male and female subjects, but only the decrease in female subjects reached statistical significance. These findings are indicative of the adaptive changes in renal function in response to acid insult [54]. In acidosis, the kidneys do not excrete $HCO_3$ into urine but reabsorb all of it and even produce new $HCO_3$, which is added to the extracellular fluid.

The kidneys consequently reduce the extracellular fluid $H^+$ concentration through 3 functional mechanisms; hydrogen secretion, re-absorption of filtered $HCO_3$ and production of new $HCO_3$. These could explain the non-significant changes in serum $HCO_3$ levels and the decrease in urinary pH observed in the exposed subjects when compared with the unexposed subjects. The decrease in urinary pH levels in exposed subjects demonstrates the kidneys' role in urine acidification to rid the body of excess acid load. This response includes the reduction if not the elimination of all $HCO_3$ from the urine as well as increase in titratable acids (i.e., phosphoric acid, creatinine and uric acid) and ammonium excretion.

Alternatively, the reactive metabolites can cause Oxidative Stress (OS) and through several patho-physiological processes lead to damage in renal structures, thereby disrupting their functional integrity such as damage to the membrane lipid bilayer and proteins, causing alteration of the normal structure of renal cells and tissues.

There could be associated impairment in several renal endpoints including regulation of water and electrolyte balance, excretion of waste products of metabolism and modulation of erythropoiesis. Accordingly, Azeez et al [51] reported increased renal tissue Malondialdehyde (MDA) and decreased Glutathione (GSH), Superoxide Dismutase (SOD) and Catalase (CAT) activities of renal tissue homogenate in animals exposed to petroleum hydrocarbons.

In a previous and present study, exposure to gasoline compounds caused a significant elevation in serum MDA, an end product of lipid per oxidation and a surrogate marker for oxidative stress [52], while a corresponding decrease in oxidative stress enzyme SOD activity was observed [55].

Exposure to petroleum products has been shown to cause immune system dysfunction [53] leading to immune perturbation, induction of auto-immune reaction, accumulation of immune complexes in the kidney tissues and causing kidney damage. Other postulated mechanisms underlying gasoline compound-mediated kidney damage include β-lyase mediated bio-activation of halogenated hydrocarbons [56]. The alpha 2μ globulin-mediated pathway that leads to nephropathy in male rats has also been implicated [56]. Besides the direct nephrotoxic effects of gasoline compounds, derangement of other biochemical indices, including hematological, hormone and lipid sub-fraction, which can secondarily affect kidney function and vice versa, have also been reported. For example, excess circulating haem caused by solvent-induced rhabdomyolysis or haemolysis of red blood cells has been posited to cause acute tubular necrosis and renal failure [56]. In agreement with this hypothesis, Ngajilo and Ehrlich [57], in a recent study reported a case of rhabdomyolysis with acute tubular necrosis and renal failure in a steel water tank cleaner exposed to a mixture of organic solvents containing toluene, xylene, acetone, hexane, benzene and methylisobutyl ketone.

In addition, the presence of metabolic acidosis in the gasoline-exposed workers could have secondarily contributed to the decline in renal function through stimulation of adaptive mechanisms aimed at restoring acid-base homeostasis. These mechanisms are detrimental to renal endpoints and include production of ammonia (ammoniogenesis) [58] and subsequent generation of new bicarbonate. It has been shown that ammoniogenesis leads to activation of the third component of complement (C3) through an alternative pathway, and subsequent reaction of ammonia with C3 triggers the alternative complement pathway, leading to progressive kidney damage.

Similarly, production of new bicarbonate in the kidney alkalinizes the interstitium [41], resulting in calcium ($Ca^{2+}$) precipitation and causing kidney damage. Furthermore, there is increased renal endothelin-l activity and activation of the Renin-Angiotensin System (RAS). Increase RAS activity leads to increased aldosterone production. Excess aldosterone production leads to haemodynamic changes, a reduced Glomerular Filtration Rate (GFR), and by extension, a decline in other renal function.

The demonstrated ability of petroleum hydrocarbons to induce oxidative stress, inflammation, and immune system dysfunction has supported the major role of gasoline in nephrotoxicity and hematotoxicity as reported in the present and previous studies.

However, unlike the previous studies [45,50,51] the strength of the present study lies on the fact that renal function were actually measured using prediction formulas to determine eGFR, a surrogate marker of renal function. This is the most widely used method of measuring renal excretory function in routine clinical practice [25] and values correlate well with Crcl in 24 h urine collection [21]. It is superior to 24 h urine Crcl altogether [59]. Therefore, isolated use of serum creatinine concentration as done by previous investigators may not reflect the actual degree of renal function in some patients due to the effect of several covariates on serum Cr concentration. Also, it is observed that the inverse relationship between serum Cr and GFR is non-linear.

The significant decreases in several erythropoiesis-modulated haemocytic variables (RBC, PCV, HB, MCHC, MCH and MCV) and

the non-significant changes in total WBC counts and WBC lineage cell (NEU and BASO) counts provide supportive evidence to previous studies that demonstrated a close association of exposure to gasoline compounds with haematotoxicity in humans [60].

Interestingly, the present results suggest a greater effect of gasoline-induced haematotoxicity on several erythropoiesis-modulated haemocytic variables as reported previously [61]. Given the significant role of the kidney in red blood cell production, it is plausible that this function of the kidney was impaired along with other renal function and in particular, impairment in synthesis and release of Erythropoietin (EPO), an acidic glycoprotein hormone that controls erythropoiesis [62,63]. However, the bone marrow-suppressive effect of gasoline constituents could have contributed to the observed changes in blood cells following exposure to gasoline compounds.

## Conclusion

Indeed, exposure to petroleum products maybe associated with significant decrease in eGFR, serum and urinary pH, normal serum AG, positive urinary AG, azotemia, electrolyte abnormalities and hematotoxicity, features suggestive of renal tubular acidosis. Preventive measures to limit exposure and increase awareness of workers on the effect of exposure to petroleum products on renal endpoints are needed.

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