CIRCULATING KIDNEY INJURY MOLECULE-1 (KIM-1) AS AN EARLY PREDICTOR OF CHRONIC GASOLINE EXPOSURE-INDUCED NEPHROTOXICITY IN MINIA CITY, MINIA, EGYPT

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ABSTRACT

Long-term exposure to gasoline had been proved to induce nephrotoxicity among gasoline handlers. This study evaluated the efficiency of using circulating kidney injury molecule 1 (KIM-1) as an early predictor of nephrotoxic effect of long-term occupational exposure to gasoline in Minia city. Eighty three male subjects were involved and were divided into 4 groups: group I: 20 apparently healthy subjects with no history of long-term gasoline exposure, group II: 19 gas station workers for a period of 1 years ± 2 months, group III: 27 gas station workers for a period of 3 years ± 2 months, and group IV: 17 gas station workers for a period of 5 years ± 2 months. All subjects were investigated for blood urea nitrogen (BUN), serum creatinine (S.Cr.) and KIM-1. The levels BUN and S.Cr. of the subjects of group III were within normal with no significant differences when compared to those of groups I and II while the level of KIM-1 was significantly increased when compared to groups I and II. The levels BUN, S.Cr. and KIM-1 of group IV subjects were significantly elevated when compared to other groups. Also, there was a positive correlation of the level of S.Cr. to the levels of KIM-1 among group IV. It is important to use protective measures at these stations, and to develop a more safe fuel in the near future as long-term exposure to gasoline may carry the risk of nephrotoxicity. KIM-1 may be a promising early predictor of such nephrotoxic effects.

Keywords: Nephrotoxicity, gasoline, gas stations, blood urea nitrogen, serum creatinine, kidney injury molecule 1 (KIM-1).

INTRODUCTlON

Gasoline exposure may induce many multi-systemic health hazards including respiratory disorders (Midzenski et al., 1992), urinary tract disorders, including prostate trouble (Dagg et al., 1992), skin rashes, eczema, or other skin allergies (Avis and Hutton, 1993), cancers (Lagorio et al., 1994), cardiovascular disorders (Yin et al., 1994), immunotoxicity (McMurry et al., 1994a) and neurotoxicity (Khalaf et al., 2004).

During refueling, people may easily be exposed to extremely high levels of gasoline vapor for a short time, although such exposure takes on more importance in the case of gas station workers (Periago and Prado, 2005).

According to a previous study, it has been found that long-term gasoline exposure resulted in altered renal functions in the form of elevated blood urea nitrogen, serum creatinine, β_2 microglobulin (β_2MG) and cystatin C. These changes were reported to take place after 5-10 years (Khalaf and Abdel Raheim, 2004).

Kidney injury molecule 1 (KIM-1) is a transmembrane glycol-protein that is highly expressed in kidney proximal tubular cells with kidney injury (Ichimura et al., 1998). The KIM-1 ectodomain is cleaved, released into urine, and can be quantified as a sensitive and specific biomarker for acute kidney injury (AKI) in rodents and humans (Ichimura et al., 2004; Koyner et al., 2010). KIM-1 reports AKI secondary to a wide range of toxic, ischemic, and septic insults. Urinary KIM-1 has undergone formal qualification review and has been qualified by regulatory agencies to be used to support preclinical drug discovery programs (Vaidya et al., 2010). In relation to liver disease, urinary KIM-1 is elevated in patients with cirrhosis with a clinical diagnosis of acute tubular necrosis more than in those with hepat-

orenal syndrome and may, with development, have utility as a diagnostic biomarker (Belcher et al., 2014). Sabbisetti et al. (2014) demonstrated that KIM-1 is released into the circulation where it reports kidney injury in mice, rats, and humans with AKI and chronic kidney disease (CKD).

In this current research, we build on the work reported by Sabbisetti et al. (2014) and investigated the hypothesis that measurement of circulating KIM-1 in case of chronic gasoline exposure can represent an early and valuable predictor of patient nephrotoxicity.

SUBJECTS AND METHODS
Subjects :
Eighty three male subjects aging 21-42 years were involved in this study.

Clinical protocol: The subjects were divided into 4 groups as follows:

Group I: consists of 20 normal subjects with no history of long-term gasoline exposure.

Group II: consists of 19 gas station workers with daily exposure to gasoline for a period of 1 year ± 2 months.

Group III: consists of 27 gas station workers with daily exposure to gasoline for a period of 3 years ± 2 months.

Group IV: consists of 17 gas station workers with daily exposure to gasoline of a period of 5 years ± 2 months.

Inclusion criteria include; apparently healthy subjects within age group (18-45) years old and gas station workers with daily exposure to gasoline of different periods of 1, 3, and 5 years.

Exclusion criteria:

All subjects with a history of previous renal disorders, hypertension, diabetes, or malnutrition were excluded from this study.

Blood collection and separation: After taking their written consents, venous blood samples (5 ml) were drawn from the patients and control, were kept into a clean dry centrifuge tubes and left to stand for few hours before centrifugation to avoid hemolysis. Serum was separated.

Biochemical analysis:

All subjects were investigated for renal function tests including blood urea nitrogen (BUN), serum creatinine (S.Cr) and KIM-1.

1. Blood urea nitrogen and serum creatinine levels: both were measured spectrophotometrically using Spekol II Carl-Zeiss spectrophotometer (Chany and Marbach, 1962; Bulter, 1978).

2. Plasma KIM-1 quantification: plasma KIM-1 concentrations were measured using microsphere-based Luminex technology, as previously described for human plasma. Analytes were quantified using a 13-point five parametric logarithmic

standard curve. Inter and intra-assay variability was less than 15%. Investigators performed all KIM-1 measurements blindly and were unaware of patients' clinical characteristics (Sabbisetti et al., 2014).

Statistical analysis:

Data were checked, coded, entered and analyzed using SPSS (version 17.0 software). The results were expressed as means ± S.D. Comparisons and correlations were done using the ANOVA and Pearson's correlation tests, with statistical significance assured at $p < 0.05$.

Human rights:

All procedures followed were in accordance with the ethical standards of the Medical Ethical Committee at National Research Centre, Cairo, Egypt and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from all patients for being included in this study.

RESULTS

Mean values of BUN, S.Cr. and KIM-1were illustrated in figures 1, 2, 3 respectively and table 1. The results of the current study revealed that all investigated parameters were within normal range in the subjects of group II with no statistical significance when compared to those of group I (Table 2).

In addition, the levels BUN and S.Cr. of subjects of group III were within normal with no significant differences when compared to those of groups I and II, while the level of KIM-1 in group III was increased significantly when compared to groups I and II (Table 2).

Table 2 shows that the levels BUN, S.Cr. and KIM-1 of subjects of group IV were significantly elevated when compared to those of group I, II and III.

A positive significant correlation between levels of (S.Cr. & BUN) and KIM-1 levels among the subjects of group IV as shown in table 3 and fiures 7 & 11 respectively. On the other hand, positive insignificant correlation between levels of (S.Cr. & BUN) and KIM-1 levels were observed among the subjects of groups II and III (Table 3 and Figures 5, 6, 9, 10). Negative insignificant correlation was noticed between levels of (S.Cr. & BUN) and KIM-1 levels among the subjects of group I (Table 3 and Figures 4, 8).

Table (1) : Mean and standard deviation values of blood urea nitrogen (BUN), serum creatinine (S.Cr.) and kidney injury molecule 1(KIM-1) in the different investigated groups (n: 83).

Parameter	Groups							
	I (n=20)		II (n=19)		III (n=27)		IV (n=17)	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
BUN (mg/dl)	13.35	1.23	14.47	0.62	18.24	1.29	27.91	2.43
S. Cr. (mg/dl)	0.71	0.08	0.79	0.07	0.84	0.09	0.97	0.12
Kim-1 (pg/ml)	64.72	3.57	65.39	4.12	73.82	4.73	78.35	5.66

S.D.; (standard deviation), n: (number of cases), group I: control group; group II: workers with a daily exposure to gasoline for 1 year ± 2 months; group III: workers with a daily exposure to gasoline for 3 years ± 2 months; group IV: workers with a daily exposure to gasoline for 5 years ± 2 months.

Table (2) : ANOVA-one way statistical analysis of the different investigated groups regarding blood urea nitrogen (BUN), serum creatinine (S.Cr.) and kidney injury molecule 1 (KIM-1) (n: 83).

Parameter	Groups	Groups					
		II		III		IV	
		f-value	p	f-value	p	f-value	p
BUN	I	0.09	0.739	0.130	0.675	2.49	0.00*
	II			0.92	0.713	2.59	0.000*
	III					0.69	0.011*
S. Cr.	I	0.02	0.277	0.09	0.073	0.18	0.000*
	II			0.07	0.062	0.16	0.000*
	III					0.04	0.057
KIM-1	I	0.03	0.743	0.42	0.000*	0.67	0.000*
	II			0.45	0.000*	0.70	0.000*
	III					0.25	0.002*

n (number of cases), group I: control group; group II: workers with a daily exposure to gasoline for 1 year ± 2 months; group III: workers with a daily exposure to gasoline for 3 years ± 2 months; group IV: workers with a daily exposure to gasoline for 5 years ± 2 months; *: significant at p value<0.05.

Table (3) : Pearson's correlation test of BUN and serum creatinine to KIM-1 in the different groups (n: 83).

Parameter	KIM-1							
	Group I		**Group II**		**Group III**		**Group IV**	
	r-value	**p**	**r-value**	**p**	**r-value**	**p**	**r-value**	**p**
BUN	-0.260	0.469	0.160	0.514	0.352	0.072	0.957	<0.001*
Serum Creatinine	-0.389	0.267	0.164	0.503	0.302	0.126	0.926	<0.001*

n: (number of cases), group I: control group; group II: workers with a daily exposure to gasoline for 1 year ± 2 months; group III: 21 workers with a daily exposure to gasoline for 3 years ± 2 months; group IV: workers with a daily exposure to gasoline for 5 years ± 2 months; *: significant at p value<0.05.
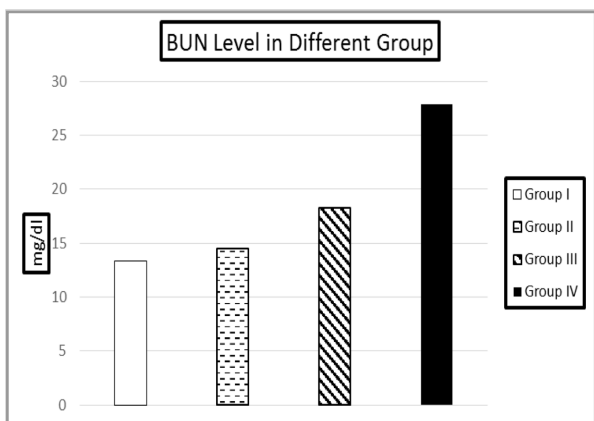
Fig. (1) : Mean values of blood urea nitrogen (BUN) in different groups (mg/dl).
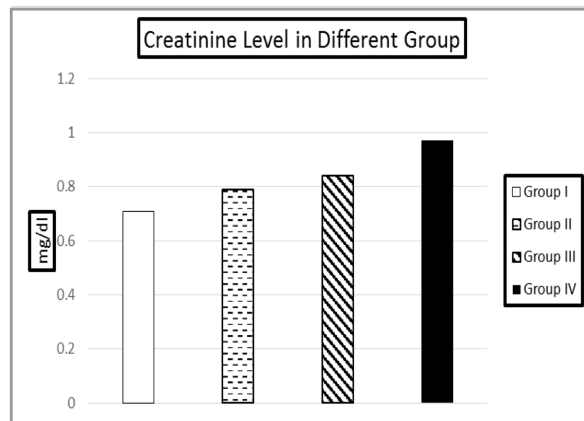

Fig. (2) : Mean values of Creatinine in different groups (mg/dl).
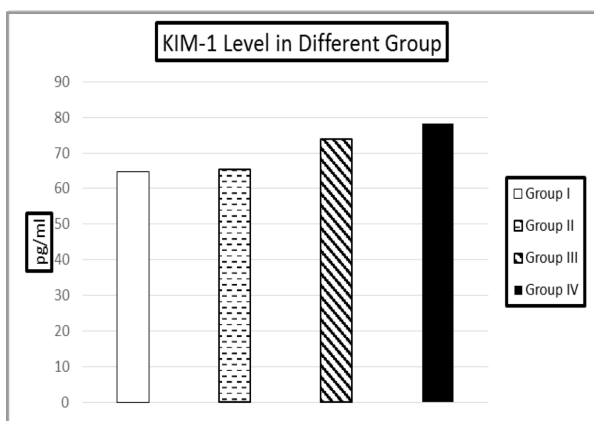

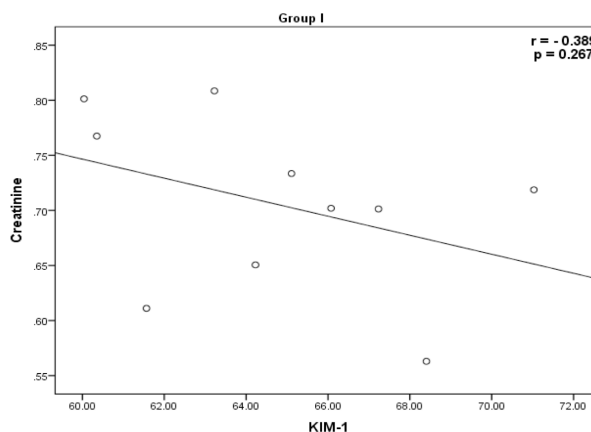**Fig. (3) :** Mean values of kidney injury molecule-1 (KIM-1) in different groups (pg/ml).

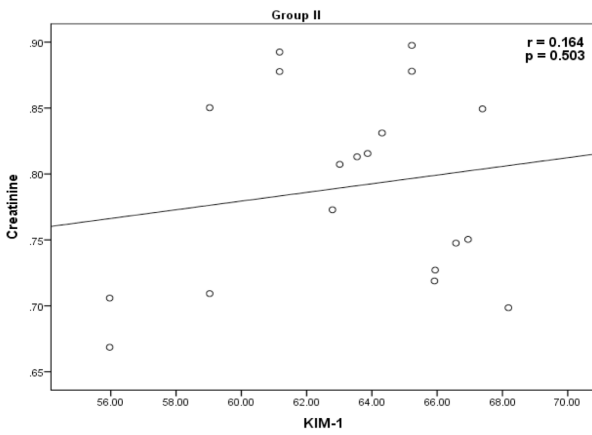**Fig. (4) :** Correlation graph of serum creatinine to KIM-1 in the group I.

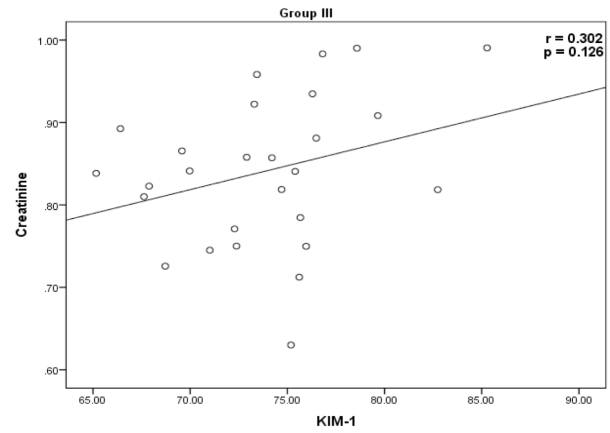**Fig. (5) :** Correlation graph of serum creatinine to KIM-1 in the group II.

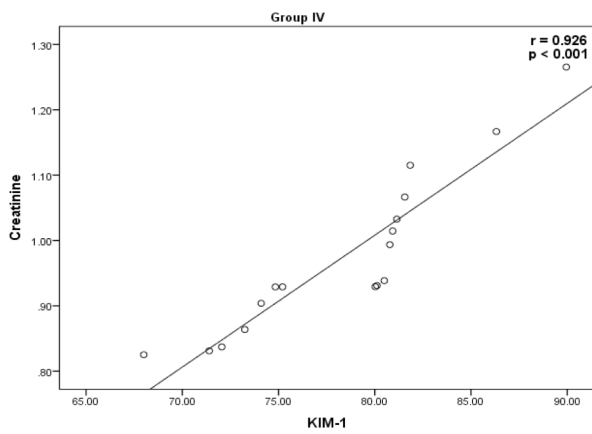**Fig. (6) :** Correlation graph of serum creatinine to KIM-1 in the group III.

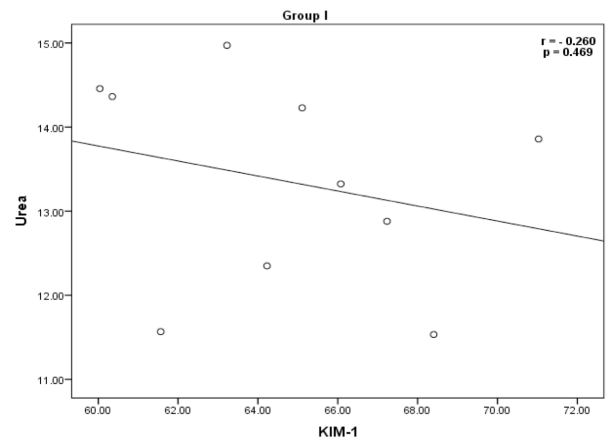**Fig. (7) :** Correlation graph of serum creatinine to KIM-1 in the group IV.

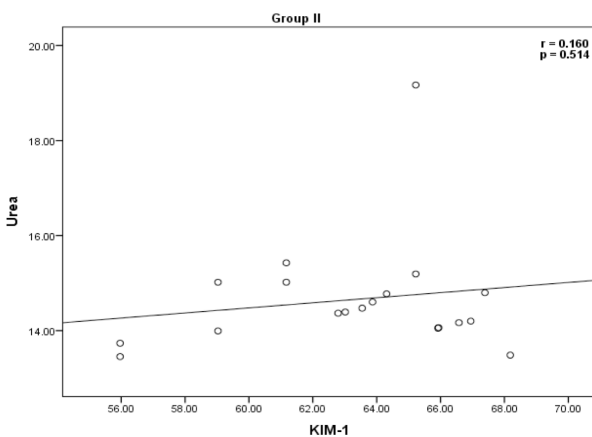**Fig. (8) :** Correlation graph of blood urea nitrogen to KIM-1 in the group I.

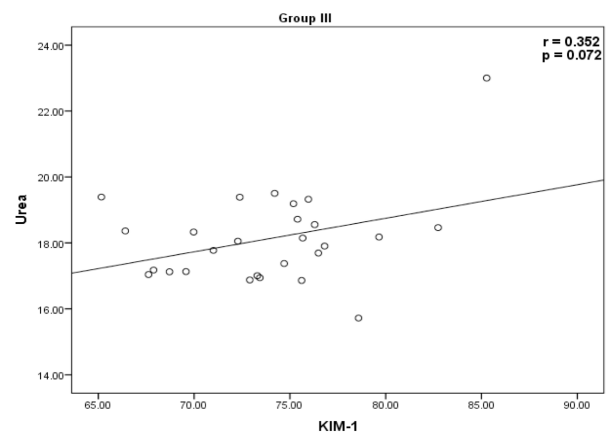**Fig. (9) :** Correlation graph of blood urea nitrogen to KIM-1 in the group II.

Fig. (10) : Correlation graph of blood urea nitrogen to KIM-1 in the group III
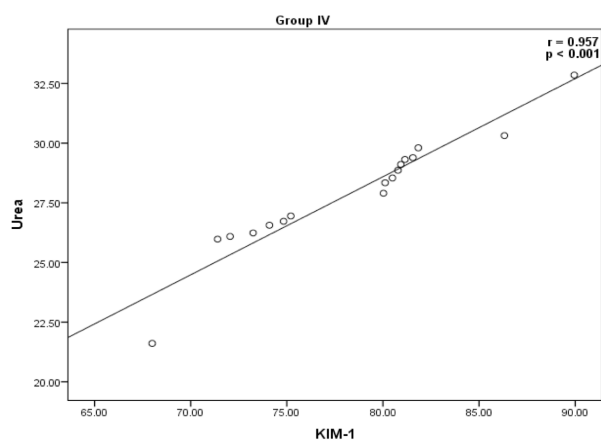
Fig. (11) : Correlation graph of blood urea nitrogen to KIM-1 in the group IV.

DISCUSSION

Gasoline and its components; benzene, toluene, and xylene; as well as the additives: ethanol, methanol, and methyl tertiary butyl ether, are moderately to mildly toxic at acute doses. Because of their volatility, these compounds are not extensively absorbed dermally unless the exposed skin is occluded. Absorption through the lungs and the gastrointestinal tract is quite efficient (Verma and des Tombe, 2002).

In the past, benzene in gasoline has been quite high, but now, there is a distinct trend in North America and Europe to reduce benzene in gasoline to a level of about 1%. The reduction of benzene in gasoline results not only in lowering of occupational exposure for workers, but it also has far greater influence in decreasing the environmental benzene exposure for the general public. However, the other

chemical constituents and impurities are still high (Dong-mei, et al., 2009).

The results of the current study showed that the levels of BUN and S.Cr. levels of the workers exposed to gasoline for 1-3 years (groups II & III) were normal with no significant difference when compared to those of group I. On longer exposure periods (5 years), there was a significant elevation of all measured parameters when compared to those of the groups I, II and III. These results revealed that nephrotoxicity due to chronic exposure to gasoline, is time dependent. These findings met the earlier reports that suggested that gasoline may induce renal function alterations due to recurrent urinary tract infections (Ishola et al., 2006). As a result of alteration of the immune system and/or chronic urinary tract irritation; benzene is known to adversely affect both humoral and cellular acquired immunity. Although the literature is too sparse to draw conclusions about any associations between gasoline exposure and the development of kidney disease, it definitely supports the impact of gasoline, and its constituents, on both humoral and cellular acquired immunity. Whether the increased reporting of urinary tract disorders is related to that effect is unknown (Cox, 1991 and Vestey, 1991).

Nowadays, the limitations of BUN and

S.Cr. as markers of the glomerular filtration rate (GFR) and tubular function are widely appreciated (Lamb et al., 2004). Based on this concept, we decided to use more recent renal function biomarker; kidney injury molecule 1 (KIM-1) whose plasma concentration reflects renal tubular injury (Sabbisetti et al., 2014).

Regarding the values of KIM-1, the results of this study reported no significant difference between groups I and II, while in groups III and IV, there were significant elevation in such values when compared to those of groups I and II. In addition, there was a positive correlation between S.Cr. to the level of KIM-1 in group IV. This indicates the presence of early chronic renal disease and reflects the superiority of KIM-1 over BUN and S.Cr. in terms of early diagnostic sensitivity in subjects chronically exposed to gasoline. This is in full agreement with many previous studies concerned with assessment of renal function in different disorders which proved this superiority that became generally accepted nowadays (Sabbisetti et al., 2014 and Antoine et al., 2015).

On the other hand, these findings are contradicting with the findings of Voss and his fellows (2005) who reported that the determination of albumin excretion in the urine appears to be a useful parameter for monitoring early renal disorders in solvent-exposed workers than many other biomarkers including; total protein, albumin, transferrin, IgG, β_2MG, retinol-binding protein, N-acetyl-beta-D-glucosaminidase, alanine aminopeptidase, β-galactosidase, β-glucuronidase, leucin aminopeptidase, alkaline phosphatase, lysozyme, Tamm-Horsfall protein and laminin fragments in urine as well as E-selectin, laminin and anti-laminin antibodies and anti-glomerular basement membrane antibodies in serum.

To our knowledge, KIM-1 has not been evaluated in subjects of chronic exposure to gasoline. No studies were located regarding renal dysfunction in humans after inhalation exposure to gasoline.

However, renal function tests were performed in two individuals who had been immersed in gasoline for several hours (Hansbrough et al., 1985). There was no evidence of abnormal renal function in either case. Pale, congested kidneys were observed in rabbits that had 8.0 mL/kg unleaded gasoline applied to their shaved skin for 12 days (Beck et al., 1983). No details regarding pathological findings were reported. On the other hand, reversible renal injury (oliguria, tubular necrosis, interstitial edema, hematuria, and reduced creatinine clearance) has been reported in a number of case reports of individuals

who accidentally or intentionally ingested gasoline (Banner et al., 1983; Kuehnel et al., 1986; Janssen et al., 1988).

Gasoline is one of a diverse group of hydrocarbons that have been shown to induce a unique syndrome of nephropathy in male rats that is associated with the accumulation of the protein, β_2u-globulin (β_2u), following acute, subchronic, or chronic inhalation and oral exposure (Olson et al., 1988; Short et al., 1989a; Short et al., 1989b).

After the discovery that gasoline caused kidney tumors in male rats but not in female rats or either sex of mice, a series of studies was undertaken to understand this sex- and species-specific disease. Investigations by Halder et al. (1984) and Halder et al. (1985) demonstrated the formation of protein droplet nephropathy by a series of branched aliphatic hydrocarbons. One of the most potent hydrocarbons causing this disease was 2, 2, 4-trimethylpentane, an important component of gasoline. The suggestion that hydrocarbon nephropathy might be related to the male rat-specific protein, α_{2u}-globulin, was first made by Alden, who identified α_{2u} as the accumulating protein in male rats exposed to decatin and hypothesized that a similar phenomenon might occur with other hydrocarbons (Alden et al., 1984 and Alden, 1986). Since these early studies, many

additional chemicals have been shown to cause β_2u-nephropathy in male rats. None of these have caused a similar nephropathy in female rats or either sex of any other species (Swenberg et al., 1989; Borghoff et al., 1990; Karl et al., 1991). Thus, β_2u-nephropathy appears to represent a sex- and species-specific disease. Alpha α_{2u}-nephropathy is characterized by the accumulation of protein droplets in the P2 segment of the proximal tubule, subsequent single cell necrosis, the formation of granular casts at the junction of the proximal tubule and the thin loop of Henle, and the presence of regenerative tubules. With chronic exposure, there is progression of these lesions, formation of linear mineralization in the renal medulla, and an exacerbation of chronic progressive nephropathy (Swenberg, 1993).

The accumulation of β_2u is cytotoxic and results in single-cell necrosis (Burnett et al., 1989; Short et al., 1989a; Dietrich and Swenberg 1991). The exfoliated renal epithelium, which represents the nidus for granular cast formation, is restored by compensatory cell proliferation. This increase in cell proliferation is localized in the P2 segment of the nephron and to a much lesser extent in the P3 segment (Short et al., 1986; Short et al., 1987; Short et al., 1989a). Increased cell proliferation can be readily demonstrated using pulse (Short et al., 1986) or continuous adminis-

tration of [3H]-thymidine or bromodeoxyuridine (Short et al., 1989a; Dietrich and Swenberg, 1993). It can be detected as early as 3 days after exposure to β_2u-inducing agents, and has been demonstrated to remain elevated through at least 50 weeks of exposure to gasoline. The increase in proliferation is dose related and necessitates the presence of large amounts of androgen-dependence β_2u-globulin. The increase in cell proliferation associated with α_{2u}-nephropathy is reversible (Short et al., 1989a; Dietrich and Swenberg, 1991). After exposures of up to 3 weeks to gasoline, proliferation returns to control rates within 1 week after cessation of exposure. Longer-term exposures result in a slower return to control rates. Morphologic evidence of regenerative tubules can still be identified 4 weeks after subchronic exposure ceases (Halder et al., 1984; Halder et al., 1985).

CONCLUSION

In conclusion, chronic exposure of the gas station workers to gasoline may carry the risk of nephrotoxicity. This raises the importance of increasing the safety measures at these stations including the establishment of workers registry and insurance system, the use of protective measures (gloves, masks, clothes, …etc), mandatory periodic vacation, regular informatory seminars with the workers, respecting the maximum allowable concentration and time, periodic medical and laboratory examination, and treating the diseased persons as early as possible, specially those with renal diseases. It is a hope to develop a more safe fuel in the near future.

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جزيء اصابة الكلية-١ المتجول كمتنبأ مبكر للتسمم الكلوي الناتج من التعرض المزمن للجازولين بمدينة المنيا – جمهورية مصر العربية

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يؤدي التعرض للجازولين لفترات طويلة الى التسمم الكلوي للمتعاملين معه. صممت هذه الدراسة لتقييم كفاءة استخدام جزيء اصابة الكلية-١ المتجول (KIM-1) كمتنبأ مبكر لتأثير الجازولين السام على الكلية نتيجة التعرض الوظيفي لفترات طويلة للجازولين في مدينة المنيا.

تضمنت الدراسة عدد٨٣ من الأشخاص الذكور تراوحت أعمارهم بين ٢١- ٤٢ سنه وتم تقسيمهم الى اربعة مجموعات: المجموعة الأولى (الضابطه): اشتملت عدد ٢٠ شخص صحيح ظاهريا بدون اي تاريخ سابق للتعرض الطويل للجازولين وبدون اي خلل في الدم او الكلى او الكبد. المجموعة الثانية: اشتملت عدد ١٩ شخص من عمال محطات الوقود وبفترة تعرض يومية للجازولين سنه ± شهر. المجموعة الثالثة: اشتملت عدد ٢٧ شخص من عمال محطات الوقود وبفترة تعرض يومية للجازولين ٣ سنين ± شهرين. المجموعة الرابعة: اشتملت على عدد ١٧ شخص من عمال محطات الوقود وبفترة تعرض يومية للجازولين لمدة ٥ سنين ± شهرين. تم قياس مستوى اليوريا والكرياتينين وجزيء اصابة الكلية-١ المتجول (KIM-1) وقد اظهرت نتائج البحث أن مستويات اليوريا والكرياتينين فى المجموعة الثالثة كانت في حدود المستويات الطبيعيه وبدون اي اختلافات مهمة احصائيا عند مقارنتها بنتائج المجموعة الأولى والثانية بينما كانت هناك زيادة في مستوى جزيء اصابة الكلية-١ المتجول (KIM-1) عند مقارنتها بنتائج المجموعة الأولى والثانية. كانت مستويات اليوريا والكرياتينين وجزيء اصابة الكلية-١ (KIM-1)   فى المجموعة الرابعة مرتفعة احصائيا عند مقارنتها بنتائج المجموعة الأولى و الثانية والثالثة. كما وجدت علاقة ايجابية بين مستوى الكرياتينين ومستوى جزيء اصابة الكلية-١ (KIM-1) بين أشحاص المجموعة الرابعة.

وقد خلصت الدراسة الى أن تعرض عمال محطات الوقود الطويل للجازولين يحمل مخاطرة التسمم الكلوي وهذا يرفع أهميـة استخـدام اجراءات الوقاية والأمان في هذه المحطـات وتطوير وقـود اكثر امانا فـي المستقبل القريب. من الممكـن أن يكـون جـزيء اصابة الكلية-١ (KIM-1) متنبأ مبكر وواعد للتسمم الكلوي.