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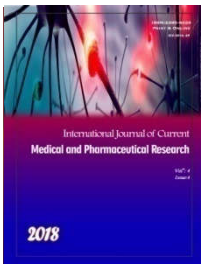

DIFFERENCES IN NON-ALCOHOLIC FATTY LIVER DISEASE PREVALENCE BETWEEN PETROL STATION WORKERS AND NON EXPOSED SUBJECTS

Sanja Brekalo-Lazarevic[1,4]., Aida Begic[2]., Ivana Lazarevic[1]., Zahida Ademovic*[3] and Suljo Kunic[4]

[1]Faculty of Medicine, University of Tuzla, Univerzitetska 1, 75 000 Tuzla, Bosnia and Herzegovina
[2]Faculty of Pharmacy, University of Tuzla, Univerzitetska 8, 75 000 Tuzla, Bosnia and Herzegovina
[3]Faculty of Technology, University of Tuzla, Univerzitetska 8, 75 000 Tuzla, Bosnia and Herzegovina
[4]Public Health Institution, Health Centre "Dr Mustafa Sehovic", 75000 Tuzla, Bosnia and Herzegovina

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ABSTRACT

Introduction: Recent studies indicate that occupational exposure to organic solvents may be an independent risk factor for the development of non-alcoholic fatty liver disease.The aim of this study was to determine the prevalence of non-alcoholic fatty liver diseaseand non-alcoholic fatty pancreas disease in a group of petrol station workers.

Methods: The study included 90 male subjects, 64 petrol station workers and control group of 26 administrative workers (non-exposed group) of the similar age and a body mass index of. All subjects underwent abdominal ultrasonography scanning, biochemical testing of blood and BMI measurement.

Results: Hepatic steatosis was more prevalent and significantly different in petrol station workers compared to controlgroup, whilst pancreatic steatosis was more prevalent though no significant different. There is no statistically significant difference in performed liver function tests of petrol station workers and control group. The median values of glucose, AST, ALT and GGT were within the limits of reference values, whereas cholesterol and triglycerides levels were elevated in both groups.Blood count revealed significant difference in the number of RBCs and the level of hemoglobin, hematocrit and MCV of petrol station workers compared to control group with the above reference values of RBCs, hemoglobin and hematocrit level.

Conclusion: The results indicate that non-alcoholic fatty liver disease can be developed as a work-related disease. Regular medical examinations of the liver function and promotion of a healthy lifestyle is recommended for the exposed workers in order to prevent possible permanent damages.

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INTRODUCTION

Increasing prevalence of non-alcoholic fatty liver disease (NAFLD) is raising awareness worldwide for the potential harmful impact on individual health. NAFLD is recognised as the most common cause of hepatic dysfunction in the general population[1,2]. Its prevalence is estimated to be 20-30% in general population of Western countries[3]. However, there is little evidence regarding its possible link to chronic occupational exposure to organic solvents. NAFLD is characterized by an increased accumulation of fat in the liver without excessive alcohol consumption as the causative factor. It is strongly associated with obesity as obesity causes hepatic insulin resistance and altered lipid synthesis[4]. The deranged metabolism is further associated with the accumulation of fatty acids and triglycerides within the liver i.e. metabolic syndrome[5]. Diabetes mellitus and viral hepatitis are also associated with NAFLD. Other factors such as age, race and gender may also modify the risk of accumulation of fat in the liver[6-8]. Identifying patients with advanced disease is a clinical challenge in primary care, because of the indolent asymptomatic nature of NAFLD. Primary care practitioners are often faced with abnormal liver function tests (LFT) in patients without clinical signs or symptoms of liver disease. The most common signs and symptoms are fatigue and right upper quadrant discomfort, which refers patients to ultrasonography scanning examination for falsely suspected gallstone disease. During physical examination there are no pathogenomic signs and the most common abnormalities are obesity and hepatomegaly, which has been reported in up to 50% of subjects. It is expected, because of the alarming growth of obesity and type 2 diabetes, that the burden of NAFLD on primary care will continue to rise[1].

Studies indicate that occupational exposure to organic solvents may play a role in the development of NAFLD[9,10]. Liver

Corresponding author:* **ZahidaAdemovic
3Faculty of Technology, University of Tuzla, Univerzitetska 8, 75 000 Tuzla, Bosnia and Herzegovina

susceptibility to chemical injury is a result of its unique position within the circulatory system and the main involvement in the biotransformation of chemicals within the body. Thus the liver injury is associated with occupational exposure to a wide variety of industrial chemicals such as solvents and other halogenated hydrocarbons, volatile organic mixtures, persistent organic pollutants, pesticides and some nitro-organic compounds[11]. Petrol is a complex mixture of organic compounds that contains at least 15 hazardous chemicals in various amounts, including benzene, toluene, xylene and naphthalene. Petrol station workers are exposed to petrolat the workplace through inhalation of its vapors or skin contact. Air level up to 99 ppm was measured at petrol station during filling of a car's tank[12]. Most of the petrol breathed in or swallowed is breathed out unchanged, but a portion that enters blood is metabolized in liver into several different chemical substances. Many of the harmful effects seen after exposure to petrol are due to individual chemicals in petrol mixture. Effects on the nervous system and the lungs were previously recorded whereas no effects on the gastrointestinal system were observed in humans after inhalation exposure to petrol[12]. Animal studies indicate that chronic exposure to unleaded petrol vapors exhibits neurotoxicity[13]and hepatotoxicity[14]. There are some studies regarding hepatic effects in humans after inhalation exposure to petrol. Sia *et al*. found that fatty liver and chronic hepatitis were the major chronic liver diseases in oil-refinery workers in Taiwan[15]. Neghab *et al*. reported that "subtle, subclinical and prepathologic early liver and kidney dysfunction was evident" in individuals exposed to unleaded petrol[16].

Lipid deposition in the pancreas has also recently gained attention[17]. Non-alcoholic fatty pancreas disease (NAFPD) is specifically defined as pancreatic fat accumulation in the absence of significant alcohol consumption[18]. Both NAFLD and NAFPD are strongly associated with obesity. Furthermore, pancreas seems to be more susceptible to fat deposition compared to the liver. There are limited data on the prevalence of NAFPD in the geneal population because of the lack of standard screening tools. Wu *et al*. reported that compared with healthy controls, those with fatty pancreas had higher levels of several metabolic risk factors (including higher values of BMI, waist circumference, triglycerides, fasting plasma glucose, hemoglobin A1c and systolic blood pressure)[19].

The aim of this study was to determine the prevalence of NAFLD and NAFPD occurrence in a group of petrol station workers chronically exposed to several volatile organic solvents taking into account their possible synergistic effect along with other risk factors. One of the objectives was to assess the results of LFTs and to evaluate to which extent abnormal LFT results are linked to fatty liver occurrence. In order to ascertain that exposure to organic solvents from petrol might represent an independent risk factor for NAFLD occurrence, obese and diabetic subjects were not included in the study.

It is very important to diagnose initial liver changes and take early preventive action, as at longer exposure of workers NAFLD may progress into severe liver injury such as fibrosis and in some cases liver cirrhosis.

MATERIALS AND METHODS

Study population

The study was carried out in the Public Health Centre "Dr Mustafa Sehovic" Tuzla, Bosnia and Herzegovina and has been approved by the Ethic committee of the Health Centre. All subjects signed informed consent. The study was designed as a cross-sectional study. The experimental group consisted of 64 petrol station workers age between 24-63 years (median age of 47±9.9). They were shift workers who work in rotating 8-hour shift schedules and are directly exposed to unleaded petrol vapors, as in Bosnia and Herzegovina petrol station workers provide the service of filling up for the customers. The control group consisted of 26 administrative workers that are not occupationally exposed to organic solvents, age between 33-65 years (median age of 47±10).

Data definitions

The demographic and occupational information of all subjects were recorded and included: gender, age, bodyweight, height, body mass index (BMI) and work experience. Obese subjects were excluded (BMI $\geq$ 30 kg m^{-2}). All the subjects underwent clinical and laboratory assays that included abdominal ultrasonography scanning and biochemical measurements.

All blood samples were taken in biochemical laboratory of Occupational medicine in the Public Health Centre in Tuzla and were tested using an Automatic Biochemical Analyzer using standard laboratory procedures. The LFT profile consisted of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) activities, total cholesterol (TC) and tryglicerides (TG) levels measurements. Full blood count consisted of white blood cells (WBC), red blood cells (RBC) and platelet (PLT) count, hemoglobin (HGB), hematocrit (HCT) and mean corpuscular volume (MCV) determination.

Excessive alcohol intake was excluded. Mild and moderate alcohol consumption were defined as drinking within the guidelines, which are compliant with the maximum allowable level of alcohol consumption that can distinguish between alcoholic fatty liver and NAFLD and that refers to 2 standard drinks a day (140 g ethanol/week) for men[20].

Type 2 diabetes was defined in patients with a documented history of the disease or a recorded drug history of antidiabetic medication.

Ultrasonography scanning

Ultrasonography scanning was imaging technique used in the diagnosis of NAFLD. This technique provides remarkable sensitivity but without accurate quantification of the degree of steatosis. Ultrasonic scanning was performed by a radiologist in the Public Health Centre in Tuzla.Criteria for diagnosis of NAFLD by abdominal ultrasonic scanning were as follows: increased hepatic echogenicity compared with the spleen and kidneys, blurring of liver vasculature and deep attenuation of ultrasonic scanning signals through the right hepatic lobe.

Statistical analysis

Descriptive statistics were applied to characterise this cross-sectional study.Chi-squared test andMann-Whitney U test were performed for statistical data analysis. Clinical variables are reported as medians and IQR. Categorical variables were reported as numbers and percentages. All statistical analyses

were performed using SPSS 13.0 software. Differences were considered statistically significant for $p<0.05$.

RESULTS AND DISCUSSION

In this study the liver status and blood parameters of 64petrol station workers exposed to petrol vapour were compared to that of 26controls working in occupational settings without exposure to organic solvents. Hepatic steatosis was more prevalent and significantly different in petrol station workers compared to control (hepatic steatosis: 34.4% and 7.7% cases, respectively; p=0.0197), whilst pancreatic steatosis was more prevalent but not significantly different compared to control (31.3% and 11.5% cases, respectively; p=0.0936). The results of abdominal ultrasonography scanning are presented in Figure 1. There were no reported cases of cirrhotic appearances.

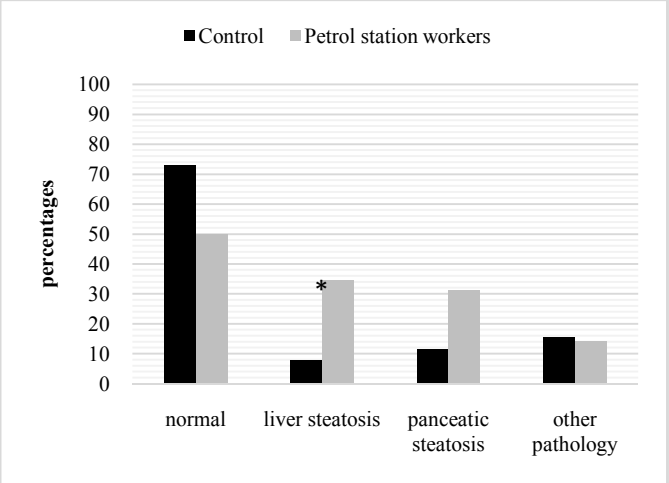

Figure 1 Abdominal ultrasonography scanning of petrol station workers (N=64) in comparison to controls (N=26).The results of diagnosed steatosis by abdominal ultrasonography scanning are presented as percentages. *Statistical significance was considered for $p \leq 0.05$.

Human and animal studies have shown that NAFPD frequently coexists with NAFLD[14], which was also confirmed in this study. Out of 64 petrol station workers hepatic and/or pancreatic steatosis developed in 26 cases (40.63%), out of which hepatic steatosis appeared in 6 cases (23.08%), pancreatic steatosis in 4 cases (15.38%) and most commonly steatosis appeared in both, liver and pancreas, in 16 cases (61.54%). In control group out of 26 subjects hepatic and/or pancreatic steatosis developed in 4 cases (15.38%), out of which hepatic steatosis appeared in 1 case (25%), pancreatic steatosis in 2 cases (50%) and steatosis appeared in both, liver and pancreas, in 1 case (25%).The study confirmed previous studies that in petrol stations as a working environment there is a risk of hepatotoxicity due to prolonged exposure to low levels of organic solvents[21,22].

The results of blood tests are shown in Table 1. Statistical analysis of blood count revealed significant difference in the number of RBCs ($p<0.0161$) and the level of hemoglobin ($p<0.0003$), hematocrit ($p<0.0001$)and MCV ($p<0.0001$) of petrol station workers compared to control group (Figures 2, 3) with the above reference values of RBCs, hemoglobin and hematocrit level (5.4 ±0.35 $x10^{12}$/L, 162.5±8.80 g/L and 0.483±0.03 L/L respectively).

There is no statistically significant difference in performed liver function tests (LFTs) of petrol station workers and control group. The median values of glucose, AST, ALT and GGT were within the limits of reference values, whereas cholesterol and triglycerides levels were elevated in both groups (petrol station workers: 5.8±1.21 mmol L^{-1} and 2.1±1.67 mmol L^{-1} and control group: 5.9±1.18 mmol L^{-1} and 1.9±1.01 mmol L^{-1}) (Table 2). Previous studies suggested that the levels of ALT and AST enzymatic activities are higher in workers exposed to organic solvents[23,24].In this study, AST, ALT and even GGT activity were not significantly different compared to control and the medians remained within the reference values (Table 1).

Cholesterol level in petrol station workers was above reference value in 40 subjects (62.5%), out of which steatosis was developed in 16 cases (40%). The level of triglycerides in petrol station workers was above reference value in 37 subjects (57.81 %), out of which steatosis was developed in 16 cases (43.24%). The results are in accordance with previous reports indicating that deranged metabolism leads to accumulation of triglycerides within hepatocytes and pancreatic cells[13].

Table 1 Blood count and biochemical blood parameters of petrol station workers (N=64) and controls (N=26).

Parameter		Median	25-75 Percentile	Minimum	Maximum	STD
WBC ($x10^9$/L)	Control	8.04	7-9.2	3.64	15.7	2.17
	Workers	7.6	6.5-9.3	4.9	15.3	2.16
RBC ($x10^{12}$/L)	Control	5.19	4.99-5.42	3.34	5.92	0.55
	Workers	5.4	5.3-5.6	4.5	6.3	0.35
HGB (g/L)	Control	154.5	148-160	125	174	11.42
	Workers	162.5	157-169.3	138	181	8.8
HCT (L/L)	Control	0.434	0.424-0.460	0.37	0.493	0.03
	Workers	0.483	0.46-0.5	0.413	0.56	0.03
MCV (fL)	Control	84.7	82.09-86.6	79.6	116	7.22
	Workers	90	87-92.1	82	99	3.88
PLT ($x10^9$/L)	Control	246.5	221.8-295.8	122	424	71.45
	Workers	237	188.5-282.3	125	351	55.7
Glucose (mmol/I)	Control	5.5	5.3-6.0	5	8.9	0.84
	Workers	5.4	5.1-5.7	4	8.4	0.77
Cholesterol (mmol/L)	Control	5.9	5.2-6.7	4.4	9.2	1.18
	Workers	5.8	4.8-6.6	3.4	8.4	1.21
Triglycerides (mmol/L)	Control	1.9	1.34-2.9	0.7	4.56	1.01
	Workers	2.1	1.5-3.4	0.7	7.8	1.67
AST (U/L)	Control	23	18.3-27.8	14	79	12.19
	Workers	20	17-24.3	11	46	5.93
ALT (U/L)	Control	42.5	36.3-52.8	18	70	13.1
	Workers	39	27.8-49.3	13	79	15.07
GGT (U/I)	Control	33	22-46	14	461	86.99
	Workers	34.5	22-47.5	14	196	34.7

The first sign of the effects of organic solvents on the liver is often difficult to notice because it does not give any subjective symptoms. In the initial stage, liver enzymes are within the limits of the reference values. At longer exposure it may progress into severe liver injury such as fibrosis and in some cases liver cirrhosis. Elevated liver enzymes are also apparent. For this reason, it is very important to diagnose initial liver changes and take early preventive action.

The limitations of this study are that there was no environmental and personal monitoring for petrol exposure, there are no records for baseline and periodic medical examination of workers to identify changes that could be attributed to petrol exposure. Also, this study is a small-scale study, which limits the generalization of results to the total population of petrol station workers.

CONCLUSION

Professional exposure to petrol vapors is an independent risk factor for the development of non-alcoholic fatty liver disease. Some laboratory parameters among petrol station workers showed changes that could be attributed to workplace exposure and should be given attention at periodic medical examination. The exposed working population requires periodic medical checkup for control of the liver function and early recognition of liver disease before development of chronic impairment should be done. Further longer term perspective studies of petrol workers are required for a more comprehensive data of long term effects of petrol exposure.

Conflicts of interests

The authors declare that they have no conflicts of interest.

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