Assessment of liver function among nickel-plating workers in Egypt

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تقييم وظيفة الكبد بين العاملين في طلاء النيكل في مصر

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الخلاصة: لا توجد تقارير متاحة حالياً في مصر عن التعرّض المهنيّ للنيكل وتأثيره على الكبد. وقد هدفت هذه الدراسة إلى تقييم وظيفة الكبد بين العمال المعرّضين مهنياً للنيكل. وقد أجريت إختبارات وظائف الكبد المعيارية لعينات من الدم مأخوذة من خمسة وعشرين من العمال الذين يعملون في الطلاء بالنيكل في مدينة دمياط المصرية، كما أُخذت عينات من ثلاثين من الموظفين الإداريين باعتبارهم مجموعة شواهد مرجعية. ثم قيست مستويات النيكل في البول بالتنظير الطيفي للانبعاث البلازمي المزدوج التحريض، فكانت هذه المستويات أعلى على نحو يُعتدُّ به إحصائياً في العمال المعرّضين للنيكل مقارنةً بالمجموعة المرجعية. وكانت مستويات ناقلتَيْ أمين الألانين والأسبرتات أعلى على نحو يُعتدُّ به إحصائياً في العمال المعرّضين للنيكل. وتَرَابَطَ مستوى الألبومين المصلي ترابُطاً سلبياً يُعتدُّ به إحصائياً مع مستويات ناقلتَيْ الأمين في المصل، في حين تَرَابَطت ناقلة ببتيد الغاما-غلوتاميل المصلية ترابُطاً إيجابياً يُعتدُّ به إحصائياً مع مستويات النيكل في البول. وهكذا فقد كانت وظيفة الكبد مُنْتَقَصَة في العاملين في الطلاء بالنيكل بالمقارنة مع العمال الإداريين غير المعرّضين للنيكل.

ABSTRACT Currently no reports are available from Egypt regarding occupational exposure to nickel and its effects on the liver. The aim of this study was to assess the liver function of workers occupationally exposed to nickel. Standard liver function tests were applied to blood samples from 25 nickel-plating workers in Damietta, Egypt and 30 administrative workers as a reference group. Levels of urine nickel, measured by inductively coupling plasma-emission spectroscopy, were significantly higher in nickel-exposed workers compared with the reference group. The levels of alanine aminotransferase and aspartate aminotransferase were significantly higher in nickel-exposed workers. The level of serum albumin was significantly negatively correlated and the levels of serum aminotransferases, and serum gamma-glutamyl-transpeptidase were significantly positively correlated with urine nickel levels. Liver function is compromised in nickel-plating workers compared with non-exposed administrative workers.

Bilan de la fonction hépatique chez les travailleurs de l'industrie du placage au nickel en Égypte

RÉSUMÉ Actuellement, il n'existe aucun rapport disponible en Égypte concernant l'exposition professionnelle au nickel et ses effets sur le foie. L'objectif de la présente étude était d'évaluer la fonction hépatique des travailleurs exposés professionnellement au nickel. Le bilan habituel de la fonction hépatique a été réalisé à partir d'échantillons de sang prélevés chez 25 travailleurs de l'industrie du placage au nickel à Damiette (Égypte) et chez 30 employés de bureau pour le groupe témoin. Les concentrations urinaires de nickel, mesurées par spectroscopie d'émission de plasma induit par haute fréquence, étaient significativement supérieures chez les travailleurs exposés au nickel que dans le groupe témoin. Les taux d'alanine amino transférase et d'aspartate amino transférase étaient nettement supérieurs chez les travailleurs exposés au nickel. Les résultats pour l'albuminémie étaient négativement et fortement corrélés aux concentrations urinaires de nickel alors que les taux sériques des transaminases et de gamma-glutamyl-transpeptidase étaient positivement et fortement corrélés aux concentrations urinaires de nickel. La fonction hépatique des travailleurs de l'industrie du placage au nickel est compromise par rapport à celle des employés travaillant dans des bureaux.

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Introduction

Nickel is a known haematotoxic, immunotoxic, hepatotoxic, pulmotoxic and nephrotoxic agent [1–6]. In the body, nickel forms a complex with adenosine triphosphate, amino acids, peptides, proteins and deoxyribonucleic acid [4]. Allergic skin reactions to nickel are also common [3].

Nickel salts are considered an industrial health hazard, since many nickel compounds reach the human environment. Occupational exposure of several million workers worldwide has been shown to give rise to elevated levels of nickel in blood, urine and body tissues. Inhalation is the primary route of occupational exposure to metals [5], although workers engaged in nickel-processing factories are exposed to nickel through inhalation, ingestion and dermal contact. Previous studies on occupational exposure to nickel during nickel-plating process reported lung damage, allergic skin reactions, renal dysfunction and histopathological changes in the nasal mucous [6].

Nickel causes increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum gamma-glutamyl-transpeptidase (SGGT) in the liver and serum of animals and humans exposed to nickel salts [7–9], indicating compromised liver function. Reported urinary nickel levels in humans can vary considerably, even in non-occupationally exposed individuals. Because of this, urine nickel is of most use when interpreted on a group basis. Reported urinary nickel concentrations in non-exposed individuals range from 0.2–10 µg Ni/L, depending on the method of analysis [10,11]. Currently, no reports are available from Egypt regarding occupational exposure to nickel and its effects on liver function. The present study was therefore undertaken to investigate a number of liver function parameters among workers in Egypt exposed to nickel during nickel-plating.

Method

Sample

The study was carried out in April 2009 and involved 55 male workers, who were divided into 2 groups. The first group consisted of 25 workers who were recruited from the nickel-plating industry in Damietta city, Egypt; this group was considered as nickel-exposed workers. They were working in 5 different workshops for nickel battery sales and repair in the same zone of the city. The second group comprised 30 office workers with no exposure to nickel and was considered as a reference group. They were working at an office in Damietta city unrelated to the nickel plating workshops. The reference group subjects were matched for age and socioeconomic status (income, area of residence) with the nickel-exposed workers. Demographic information and work history and habits of all subjects were obtained through a questionnaire.

Laboratory methods

All laboratory equipment was well cleansed by soaking in 10% nitric acid for 24 hours and rinsing thoroughly with deionized water [12]. The same cleansing procedure was applied to the polypropylene containers used for venous blood and urine sampling and for storing the serum.

Urine test

A urine sample was collected from the nickel-exposed workers in metal-free polyethylene bottles at the end of the week at the end of a shift after 6 days working with a normal 8-hour working day and a 48-hour working week. The digested samples were measured for nickel using the method of Andersen et al. [13] and inductively coupling plasma-emission spectroscopy (Plasma400 emission spectrophotometer, Perkin Elmer). The standardization of nickel was done using standard solutions of 0 to 30 mg/L (Buck Scientific). The internal standard of nickel 3 mg/L was added to urine and analysed and the recovery was found to be 98%. Nickel levels were reported as mg per g creatinine to allow for variations in urine dilution. Urinary nickel was standardized with urinary creatinine concentrations measured by the Jaffe reaction method developed by Husdan et al. [14].

Blood tests

Samples of 5 mL whole blood were collected in test-tubes at the end of the working week at the same time as urine sampling. Sample collection followed the guidelines described by Cornelis et al. [15]. Serum was separated by centrifugation at 2500 rpm for 20 min at 25 °C.

The collected serum was used to assess liver function using standard methods [16–18]. All the biochemical markers were estimated using a random access analyser (RA-50, Bayer).

Serum ALT and AST were used to assess hepatic inflammation (kits supplied by Human Gesellschaft für Biochemica und Diagnostica). Alkaline phosphatase (ALP) and SGGT were used to assess chlolestasis (kits supplied by Chema Diagnostica). The determination of serum total bilirubin was used to assess hepatic clearance (kits produced by Diamond Diagnostic). The determination of serum total protein and albumin was used to assess synthetic function of liver (protein kits produced by Chema Diagnostica; albumin kits by Human Gesellschaft für Biochemica und Diagnostica). For internal quality control human-based control sera were used (QN.0050CH, Chema Diagnostica).

Statistical analysis

Numerical data were expressed as mean and standard deviation (SD). Student *t*-test was used to compare the mean levels of parameters between the nickel-exposed and reference groups. The chi-squared test was used to compare the abnormal frequencies of liver function tests between groups. Pearson correlation coefficient was used to find the

association between urine nickel levels and liver function indicators. The level of statistical significance was established at 0.05 with a statistical power of 80%.

Results

Some background parameters of the nickel-exposed and reference groups are presented in Table 1. Due to the matching, the mean age of nickel-exposed and reference workers were similar at 41.5 (SD 2.1) and 42.4 (SD 1.9) years respectively. The nickel workers had been working in the nickel industry for a mean duration of 13.4 (SD 2.5) years. The mean level of urine nickel was significantly higher in nickel-exposed workers than the reference group [14.9 (SD 0.3) versus 3.3 (SD 0.1) mg/g creatinine respectively] ($P < 0.001$).

The results of liver function tests in nickel-exposed workers and reference workers are presented in Table 2. The mean level of ALT was significantly higher in the nickel-exposed workers compared with the reference group [101.2 (SD 6.0) IU/L versus 30.1 (SD 0.6) IU/L respectively] ($P < 0.01$). The AST level was also significantly higher [84.4 (SD 5.7) IU/L versus 21.4 (SD 0.3) respectively] ($P < 0.01$). The mean levels of serum ALP, SGGT and serum total bilirubin were higher in the nickel-exposed than the reference workers but the difference was not statistically significant. Total protein and serum albumin levels were lower in nickel-exposed workers than the reference group, but not significantly so.

Table 3 presents the correlation coefficients between urine nickel and liver function indicators among the study subjects. Positive significant correlation coefficients were found between the levels of serum ALT, AST and SGGT and urine nickel levels ($P < 0.01$). The association between urine nickel and serum albumin was also significant ($P < 0.05$).

The distribution of abnormal frequencies of liver function among nickel-exposed workers and the reference group was assessed using mean values and 95th percentiles of AST, ALT, ALP, SGGT and total bilirubin and 5th percentiles for serum total protein and the serum albumin. Table 4 shows the distribution of abnormal frequencies of liver function tests in the study subjects.

Discussion

Nickel is a widely distributed metal that is industrially applied in many forms. The level of nickel in urine is considered a biomarker of nickel exposure [19]. In our study the levels of urine nickel were significantly increased in nickel-plating factory workers compared with a reference group of administrative workers. Similar results were found in studies on nickel-plating workers in Finland and India [20,21].

Table 1 Age, duration of exposure and urine nickel level of the nickel-exposed and reference groups

Characteristics	Reference group workers ($n = 30$)		Nickel-exposed workers ($n = 25$)	
	Mean	SD	Mean	SD
Age (years)	42.4	1.9	41.5	2.1
Duration of nickel exposure (years)	0.0	–	13.4	2.5
Urine nickel level (mg/g creatinine)	3.3	0.1	14.9	0.3*

***P < 0.001.*
SD = standard deviation.

Table 2 Serum liver function markers of the nickel-exposed and reference groups

Variable	Reference group workers ($n = 30$)		Nickel-exposed workers ($n = 25$)	
	Mean	SD	Mean	SD
ALT (IU/L)	30.1	0.6	101.2	6.5**
AST (IU/L)	21.4	0.3	84.4	5.7**
Total protein (g/dL)	6.38	0.10	5.89	0.11
Albumin (g/dL)	3.65	0.07	2.96	0.05
Total bilirubin (mg/dL)	0.48	0.12	1.11	0.05
ALP (IU/L)	89.6	5.1	109.2	8.4
SGGT (IU/L)	35.9	1.6	68.5	2.2

***P < 0.01.*
SD = standard deviation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; SGGT = serum gamma-glutamyl-transpeptidase.

Table 3 Correlation between liver function markers and urine nickel levels of the nickel-exposed and reference groups

Variable	Correlation coefficient (*r*)							
	Urine Ni	ALT	AST	Total protein	Albumin	Total bilirubin	ALP	SGGT
Urine Ni	1.00							
ALT	0.63**	1.00						
AST	0.73**	0.65**	1.00					
Total protein	–0.47	–0.34	–0.72	1.00				
Albumin	–0.40*	–0.36	–0.74	0.75**	1.00			
Total bilirubin	0.31	0.59	0.57	–0.32	0.41	1.00		
ALP	0.30	0.58*	0.56*	–0.31	0.38	0.99	1.00	
SGGT	0.47**	0.65**	0.80*	–0.49	0.56	0.85	0.83	1.00

**P < 0.05; **P < 0.01*
Ni = nickel; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; SGGT = serum gamma-glutamyl-transpeptidase..

The markers of liver inflammation, i.e. serum ALT and AST levels, were significantly higher in nickel-exposed workers compared with the reference group. These results are in agreement with others, who found that nickel increased ALT enzyme activity in humans [22]. Animal studies also show significantly increased activity of serum ALT and AST enzymes following nickel treatment, which are indicative of damage to the liver parenchyma [7,8,23,24].

The markers of cholestasis, i.e. levels of serum ALP and SGGT, were higher in nickel-exposed workers compared with the reference group but the difference was not statistically significant. Our results are in agreement with Kalahasthi et al.'s study of nickel-plating workers in which blood levels of SGGT were raised, but not significantly, compared with a control group [21]. Sidhu et al. found an increase of ALP and ALT enzyme activity in rats treated with nickel sulphate [7].

Serum total bilirubin, a marker of hepatic clearance, was also higher in the nickel-exposed workers compared to the reference group, but not significantly so. The mean levels of liver function tests of the present study were similar to Kalahasthi et al.'s findings for nickel-plating workers in India [21]. The results also agree with Sunderman et al. who reported a mild transient hyperbilirubinaemia in workers with acute exposure to nickel compounds [9].

The markers of synthetic function, i.e. serum total protein and albumin, were lower in nickel-exposed workers than the reference group, but these too were not significant. In human and animal studies nickel has been shown to bind to albumin and to specific alpha-glycoproteins, which may explain its hepatic and renal toxicity [25,26]. Alveolar proteinosis has been shown in animal studies of inhaled nickel oxide [27].

In summary, we found that liver function was compromised in nickel-plating workers compared with a reference group of workers with no occupational exposure to nickel. Our findings agree with studies of nickel-plating workers in other countries and with data on nickel-induced hepatotoxicity from animal studies. We recommend that workers who may be exposed to toxic levels of nickel should be monitored in a systematic programme of medical surveillance that is designed to prevent occupational injury and disease.

Table 4 Frequency of workers with abnormal liver function tests in the nickel-exposed and reference groups

Variable	Reference group workers (*n* = 30)		Nickel-exposed workers (*n* = 25)	
	No.	%	No.	%
ALT (IU/L)	3	10.0	5	20.0
AST (IU/L)	3	10.0	5	20.0
Total protein (g/dL)	1	3.3	1	4.0
Albumin (g/dL)	1	3.3	1	4.0
Total bilirubin (mg/dL)	2	6.7	1	4.0
ALP (IU/L)	2	6.7	3	12.0
SGGT (IU/L)	1	3.3	1	4.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; SGGT = serum gamma-glutamyl-transpeptidase.

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