HYPERTHYROIDISM AMONG GALVANIZATION WORKERS DUE TO EXPOSURE TO ZINC FUMES

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ABSTRACT: The intimate relation between zinc as a trace element and the thyroid function has been extensively investigated in many studies.
Aim: This study aimed at clarifying the effect of excessive occupational exposure to zinc dust and fumes among galvanization workers on thyroid functions.
Methods: The study population consisted of 22 galvanization male workers and an equal group of matched males. Every participant of this study was subjected to occupational history taking, questionnaire on the symptoms of thyrotoxicosis, full clinical examination with special emphasis on thyroid gland examination, assessment of zinc levels in plasma and urine as exposure indices for zinc exposure and measuring thyroid function hormones namely, free thyroxin (FT4), free triiodothyronine (FT3), and thyroid stimulating hormone (TSH).
Results: Both urine and plasma zinc levels were significantly higher in the exposed group ($p<0.05$) compared to their referents. However, the zinc plasma level was not correlated with duration of work. Surprisingly, the study revealed marked significant increase in the mean values of FT4 and FT3 ($p<0.005$) with significant lowering of TSH ($p<0.05$) among the exposed group. Moreover, FT4 was in significant positive correlation with duration of work and plasma level of zinc.
Conclusion: This study points to the possibility of the occurrence of thyroid stimulation due to excessive occupational exposure to zinc dust and fumes similarly to many other studies which demonstrated enhancement of thyroid functions after increasing zinc supplementation. However, larger scale studies are recommended to verify this possibility and its mechanism.

KEY WORDS: galvanization, zinc, zinc fumes, hyperthyroidism, thyroid hormones

INTRODUCTION

The biological effects of zinc are remarkably diverse. It is a constituent of 300 enzymes, representing all six classes described by the International Union of Bio-

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Abbreviations:
FT4 = free thyroxin
FT3 = free triiodothyronine
TSH = thyroid stimulating hormone

Received:
Revised:
Accepted:

chemistry (Vallee and Falchuk, 1993). In addition, 30% of cellular zinc is found within the nucleus and a large number of proteins that play a role in the regulation of gene expression have been either shown or suspected to contain zinc (Freake et al., 2001). Zinc has close interrelationships with the endocrine system, and is essential for normal growth, reproductive function, thyroid function and favourable for the glucose metabolism. Therefore, zinc deficiency causes growth retardation, delayed sexual maturation, hypogonadism, thyroid dysfunction and impaired glucose tolerance. Conversely, a lot of hormones appear to influence the zinc status in the body (Kaji, 2001).

Just as zinc deficiency has been associated with adverse effects in humans and animals, overexposures to zinc also have been associated with toxic effects. Usually overexposure is encountered in oral ingestion of large amounts of zinc supplements (Barceloux, 1999). Recently, Piao et al. (2003) reported significant disturbances in the levels of serum glutamic oxalacetic transaminase (GOT) in a group of rats exposed to Zn acetate through intraperitoneal injections. Moreover, the authors also observed that the level of serum cortisol was increased by zinc acetate in a dose-dependent manner. Piao and his co-workers concluded that exposure to zinc, especially at higher doses, may produce toxic effects in various tissues and organs including the haematopoietic system, cytogenetics, biochemistry and endocrine system function.

However, there are many occupations involving zinc that carry the risk of excessive exposure to dusts and fumes of metallic zinc and zinc compounds (Cohen and Powers, 2000). Currently, most of the metallic zinc is used principally in galvanizing iron and steel to prevent corrosion and oxidation. This is carried out by passing the iron or steel through a molten bath of zinc at a temperature of around 860 °F (460 °C) thus coating iron or steel with a thin zinc layer (Verma and Shaw, 1991). The most frequently encountered hazard from zinc during galvanization process is exposure to zinc oxide fumes which are also emitted in any process involving molten zinc. Metal fume fever is the most common health hazard experienced among workers exposed to these zinc oxide fumes but chemical pneumonitis is also reported on rare occasions (Gordon et al., 1992; Taniguchi et al., 2003).

However, occupational exposure to zinc by inhalation can make up an amount of zinc about to be equivalent to that taken orally by food. Nevertheless, it is the zinc level of respirable particulates and absorption from the lung that will determine the amount absorbed (WHO, 2001). Recently, El-Safty et al. (2006) reported significantly lower levels of serum copper among galvanization workers with excessive exposure to zinc fumes indicated by their high serum zinc levels, pointing to the risk of developing copper deficiency by occupational exposure to zinc in one hand and to the possible risk of developing systemic health effects due to excessive occupational exposure to zinc fumes, on the other hand.

In the current study, we were informed by the occupational safety and health department affiliated to one of the major foundries, that there were 3 individuals out of 59 workers involved in the galvanization sector, found to be suffering from a condition of hyperthyroidism that necessitated a surgical thyroidectomy in 2 cases and medication in one case. Therefore, this study was designed aiming at the as-

sessment of thyroid hormones among galvanization workers and their relation to plasma and urine concentrations of zinc as an index for zinc exposure.

METHODOLOGY

This study was carried out in the galvanization sector in one of the major foundries in El Giza governorate in Egypt. The foundry was responsible for production of iron pipes and galvanization of these pipes using hot dip galvanization method. Generally, the exhaust ventilation was not working properly and most of the workers were not using protective equipment (masks, gloves) regularly. Unfortunately, measuring the concentration of zinc dust particles and zinc fumes was not feasible.

The study population comprised the working force of the galvanization sector after application of exclusion criteria which included workers receiving multi-mineral or multivitamin oral supplementations including zinc, workers underwent thyroid surgery or receiving any form of thyroid treatment. After application of exclusion criteria, 36 workers were eligible for inclusion but only 22 workers approved to participate in the study. An equal group of referents (n=22) were randomly selected from men employed in a supermarket series situated in residential areas away from factories and none of the referents was receiving any oral supplementation of vitamins or minerals. Both exposed and referent groups were matched for age, sex and socioeconomic status.

All workers were interviewed using a special questionnaire involving occupational history and full clinical examination including thyroid gland inspection and palpation.

A first morning urine sample was collected and stored in a urine container for measurement of zinc in urine. Blood specimens were obtained from cubital vein on zinc free heparin to evaluate serum zinc level. Measurement of zinc was accomplished by graphite furnace atomic absorption spectrophotometer (Perkin-Elmer model 5100PC, Norwalk, CT). Concentration of zinc in urine samples was then corrected for urinary creatinine.

Assessment of thyroid function was done by measuring free thyroxin level (FT4) and free triiodothyronine (free T3) serum levels in addition to thyroid stimulating hormone (TSH) level using ELISA technique (DiaMed EuroGen, 2300). Their values were reported as ng/dl, pg/ml and μIU/ml for free T4, Free T3 and TSH respectively.

Statistical analysis

The statistical evaluation of the results was conducted with use of the software statistical package for social sciences (SPSS) for windows 9.1 program. Unpaired Student's t-test was used to compare between the two study groups. Pearson correlation coefficient was used to relate between duration of exposure, level of plasma zinc and plasma levels of thyroid hormones. A p-value of <0.05 was considered significant.

RESULTS

The age range of the exposed workers was 22 to 55 years with a mean value of 37.5 ± 9.2 years showing no statistically significant difference when compared to the referent group (range: 25–55; mean 38.8 ± 9.5 years). The mean duration of exposure was 10.3 ± 7.5 years.

Blood level of zinc showed highly significant difference in the mean values of 18.09 ± 1.81 µmole/l and 15.30 ± 1.0 µmole/l among the exposed and the control subjects, respectively ($p<0.001$) (*Table 1*). The exposed group had statistically significantly higher concentration of zinc in urine than their referents (379.23 ± 52.66 versus 346.86 ± 36.97 µg/mg creatinine, $p<0.001$).

TABLE 1. Levels of zinc in plasma and urine and serum levels of free T4, free T3 and TSH in zinc fumes exposed and control subjects

	Exposed N=22 Mean ± s.d.	Control N=22 Mean ± s.d.	p-value*
Plasma zinc (µmole/l)	18.09 ± 1.81	15.30 ± 1.00	<0.001
Urine zinc (µg/mg creatinine)	379.23 ± 52.66	346.86 ± 36.97	0.029
FT4 (ng/dl)[1]	2.01 ± 1.23	1.132 ± 0.365	0.004
FT3 (pg/ml)[2]	5.23 ± 2.49	3.41 ± 1.02	0.004
TSH (µIU/ml)[3]	1.61 ± 1.018	2.355 ± 0.972	0.02

* statistical significance at $p<0.05$

[1] normal range of free T4 is (0.8–2.19 ng/dl)

[2] normal range of free T3 is (1.3–5.0 pg/ml)

[3] normal range of TSH is (0.4–5 µIU/ml)

The results revealed remarkable increase in the thyroid hormone levels in the exposed group (FT4: 2.01 ± 1.23 ng/dl, FT3: 5.23 ± 2.49 pg/ml), above the normal reference range (0.8–2.19 ng/dl for FT4 and 1.3–5.0 pg/ml for FT3). These levels were significantly higher than the control mean values ($p<0.005$). TSH was statistically significantly ($p<0.05$) lower among the exposed workers (1.61 ± 1.018 µIU/ml) than among the control ones (2.355 ± 0.972 µIU/ml).

The frequency distribution of abnormal patterns in the thyroid hormone functions detected among the exposed and the control groups revealed that, none of the control subjects had any abnormal pattern while four workers (18%) had a pattern of hyperthyroidism (elevated FT4, FT3, depressed TSH), one worker (4.5%) had high FT3 with low normal TSH, and high normal FT4. Two workers (9%) had low normal TSH (0.7 and 0.49 µIU/ml, respectively) and high FT3 and FT4. This means that there were 7 workers (31.5%) having abnormal pattern of thyroid function tests.

As regards symptoms and signs of hyperthyroidism among the exposed subjects, two workers out of 7 (28.5%) were suffering from weight loss. One worker (14.2%)

had heat intolerance, four workers (57.1%) had irritability, one worker (14.2%) had insomnia and 1 worker (14.2%) had palpitation. Clinical examination revealed no abnormality in thyroid gland by inspection or palpation but during a general examination two workers (28.4%) were found to have occasional extrasystole with tachycardia.

Pearson's correlation between duration of work with FT4 and TSH revealed statistically significant positive correlation with FT4 ($r=0.595$; $p<0.01$), and statistically significant negative correlation with TSH ($r=-0.484$; $p<0.05$). The relationship between duration of work and plasma level of zinc was statistically not significant. When correlating plasma zinc level with thyroid hormones, there was a statistically significant positive correlation with FT4 ($r= 0.445$; $p<0.01$).

TABLE 2. Frequency distribution of abnormal pattern of thyroid functions among exposed and control groups

	Exposed (n=22)	Control (n=22)
Cases with hyperthyroidism	4 (18%)	0
Cases with isolated ↑ FT3	1 (4.5%)	0
Cases with low normal TSH and ↑ FT4 & FT3	2 (9%)	0
Normal	15 (68.5%)	22 (100%)

TABLE 3. Correlation coefficient (r) of the duration of work and plasma level of zinc with FT4 and TSH among the exposed galvanization workers (n=22)

	FT4(ng/dl)	TSH (µIU/ml)	plasma zinc(µmol/l)
Duration (years)	r = 0.595*	r = – 0.484*	n.s
Plasma zinc	r = 0.445*	n.s	–

* Statistically significant ($p<0.05$)

DISCUSSION

While, the toxicokinetics of ingested zinc have been extensively studied, quantitative data on the absorption of zinc following inhalation exposures were not determined (ATSDR, 2005). However, the increased zinc levels demonstrated in plasma, blood and urine of occupationally exposed workers indicated that absorption from the pulmonary tract does occur (Hamdi, 1969 and Trevisan et al., 1982). Besides, some inhaled zinc is undoubtedly swallowed (and absorbed via the gastrointestinal tract) following clearance via the mucociliary mechanism (ATSDR, 2005). In fact, there is no simple measure of body burden of zinc as most of the amount of zinc in the body is located in inaccessible tissues such bones and muscles. Nevertheless, serum/plasma zinc is the most widely used index of zinc status in humans (WHO, 2001). On the other hand, little amount of zinc is found to be excreted in the urine, however, some investigators have used zinc in urine for the assessment of occupa-

tional exposure to zinc (Martin et al., 1999). In our study, both median (17.88 μmol/l) and mean values (18.09 ± 1.81 μmol/l) of plasma zinc were within the normal reference range (12.3–18.4 μmol/l), yet results showed a statistically significant increase in the serum and urine zinc levels in the exposed workers compared to their referents ($p<0.005$) which agrees with other studies investigating the same parameters in similar occupational exposure conditions (Martin et al., 1999 & Fourtes and Schenck, 2000) and suggests an increased body burden of zinc among the exposed workers.

On correlating duration of exposure to zinc with elevation of serum levels of zinc, the relation did not attain statistical significance ($p>0.05$). This goes with what was stated by ATSDR (2005) and can be explained by the fact that, only a small proportion (< 1%) of body zinc circulates in plasma while, 90% of body zinc is stored in muscles, bones, liver and kidney. Hence, plasma zinc does not necessarily reflect total body zinc content (WHO, 2001).

Many studies demonstrated the role of zinc as one of trace elements that are needed for the normal function, synthesis and metabolism of the thyroid gland (Arthur and Beckett, 1999). There are marked alterations in the zinc levels in patients with thyroid disease. Zinc level is lower in hypothyroidism and higher in hyperthyroidism pointing to the intimate relation between zinc and the thyroid gland (Leblondel and Allain, 1989 & Baltaci et al., 1999)**.** However, using MEDLINE we could not find reports on the effect of occupational exposure to zinc fumes on the thyroid gland hormones. Besides, ASTDR (2005) stated that no studies were located regarding musculoskeletal, endocrine, dermal, or body weight effects in humans or animals after inhalation exposure to zinc or zinc compounds. Surprisingly, in our study, marked significant increase in the serum level of FT3 and FT4 ($p<0.005$) was found among the zinc exposed workers accompanied by significant lowering of TSH level ($p<0.05$). This increase was due to the presence of cases (18%) suffering from hyperthyroidism and 1 case (4.5%) having increase in FT3 with normal FT4. The association between exposure to zinc and increase in the thyroid hormone levels became more evident by the positive significant correlation between free T4 and both plasma level of thyroid and duration of exposure (*Table 3*).

However, our results are parallel to many reports which claim that exogenous zinc administration activates thyroid functions. Kralik et al. (1996) reported that male Sprague-Dawley rats fed low-zinc diet for 40 days showed decreased serum concentrations of T3 and free T4 by approximately 30% compared with those fed adequate-zinc diet. In another study, the effect of melatonin which has a general inhibitory effect on thyroid hormones, was opposed by administration of zinc along with melatonin to male Sprague-Dawley rats (Baltaci et al., 2004).

Similarly, effects of zinc supplementation on thyroid function have been evaluated in humans. Wada and King (1986) measured basal metabolic rate and plasma thyroid hormones in healthy young men fed low zinc diet for 54 days and thereafter fed adequate-zinc diet for 9 days. They observed that basal metabolic rate and serum free T4 levels decreased significantly during the low zinc period, and increased during adequate-zinc period. In addition, Nishiyama et al. (1994) claimed that in

handicapped people with zinc deficiency low levels of serum free T3 and T4 returned to normal after zinc supplementation.

Other studies presented contradictory results. Dean et al. (1991) and Donmez et al. (2002) reported depressed levels of circulating thyroid hormones as well as significant reduction of the size of the follicles of thyroid gland among chicks when they were fed high zinc diet**.** This discrepancy in results may be explained by differences in the manner and type of zinc administration. In addition, in studies of zinc supplementation to winged animals and little ruminants an inhibition of thyroid hormones was found. This inhibition was found to be dose dependent and resulted from high doses (Kececi and Keskin, 2002).

However, the mechanism of the stimulatory effect of zinc on thyroid gland is incompletely understood. It is suggested that zinc application increased thymic functions and this in turn, improve thyroid functions influencing the pituitary-thyroid axis (Napolitano et al., 1990). On the other hand, the fact that the activity of 5'-deiodinase in liver fell by 67% in cases with zinc deficiency may be accepted as evidence for the importance of role of zinc in the conversion of T4 to T3, thus affecting the metabolism of this hormone (Kralik et al., 1996). The latter role of zinc was well demonstrated in another recent study (Maxwell and Volpe, 2007) where zinc supplementation to two zinc deficient, physically active females, appeared to have a favourable effect on thyroid hormone levels, particularly on total T3. This goes in accordance with our results since in addition to the exposed workers having hyperthyroidism, there was another exposed worker (4.5% of cases) who had isolated elevation in free T3 while having normal levels of serum free T4, and TSH. However, the mechanism of effect of zinc on thyroid gland function remains to be elucidated.

In most of cases, estimation of TSH level would be helpful as a first indicator that hyperthyroidism is developing and would drop to abnormally low levels (normal range 0.4–5 μIU/ml) before free T4 levels rise higher than the normal range (0.8–2.19 ng/dl). In the current study, 2 cases out of the exposed workers were found to have low normal levels of TSH (0.7 and 0.49 μIU/ml, respectively) while they were having abnormally high levels of both T4 and T3 hormones. However, sometimes TSH lags behind thyroid hormone levels and would not change to reflect this rise in free T4 for at least 6 weeks (Hueston, 2001).

Whereas, the term hyperthyroidism covers any disease that results in the production of excess thyroid hormones, thyrotoxicosis refers to the clinical, physiological and biochemical syndromes occurring when the body's tissues are exposed to that excess of these hormones (Jameson and Weetman, 2005). The major symptoms of thyrotoxicosis include palpitations, hyperactivity, anxiety, nervousness, heat intolerance, tremor, weight loss, diarrhoea, disturbances of menstruation and sweating. Common signs of thyrotoxicosis include: weight loss despite increased appetite, tachycardia or atrial fibrillation, systolic hypertension, warm and smooth skin, fine tremor and muscle weakness. Younger patients tend to exhibit more sympathetic activation, such as anxiety, hyperactivity and tremor, while older patients have more cardiovascular symptoms, such as dyspnoea and atrial fibrillation (Fisher, 2002). In our study, clinical assessment of zinc exposed workers revealed that none of the hyperthyroid workers had the full clinical picture characterizing the thyrotoxicosis pa-

tients. However, taking into consideration that the excess of thyroid hormones in our case was mild, thus the detected minimal clinical manifestations should not be surprising as each patient probably had a different sensitivity to mild excess of thyroid hormones (Biondi et al., 2000). In accordance with our findings, many studies stated that the clinical manifestations of thyrotoxicosis do not always correlate with the extent of the biochemical abnormality (Kolawole et al., 2002 and Volkov et al., 2006).

CONCLUSION

Our results suggest that excessive occupational exposure to zinc dust and zinc fumes has a stimulatory effect on thyroid functions manifested by an increase in thyroid hormone levels even if this increase was not associated with clinical manifestations of hyperthyroidism. Larger scale studies investigating this stimulatory effect of zinc on thyroid and its mechanism are to be considered.

ACKNOWLEDGEMENTS

We are grateful to Mr. Mohamed – the director of health and safety department of the foundry under study, for helping us in achieving this work.

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