The Effect of Heavy Metals on Thyroid Hormones Associated with Autoimmune Thyroid Disease

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Abstract

The purpose of this study was to discover whether or not, and to what extent, heavy metal exposure is a factor in the etiology of autoimmune thyroid disease. Because people are constantly exposed to heavy metals via the environment and diet, mercury (Hg) and lead (Pb) levels in the blood are often greater than the levels designated as safe by health organizations. At the same time, an estimated 20 million Americans have some sort of thyroid disorder, many of which are unaware of their condition. Hypothyroidism (Hashimoto’s Thyroiditis) and hyperthyroidism (Graves’ disease) are among the most common of these diseases, and the number of cases is rising each year. In this study, it was hypothesized that, because of their physiological effects, increased heavy metal levels (Hg and Pb) would cause significant changes in thyroid hormone levels associated with autoimmune thyroid disease. To test this hypothesis, data from this study’s parent study, “Elevated Blood Hg at recommended seafood consumption rates in adult seafood consumers”, was analyzed for free triiodothyronine (FT3), triiodothyronine (T3), free thyroxine (FT4), thyroxine (T4), and thyroid stimulating hormone (TSH). Participants were recruited and asked to complete surveys that analyzed their potential heavy metal exposure and demographic information. Morphometric data and blood specimens were collected at an appointment at the Clinical Research Core at Stony Brook University Medical Center in order to calculate health factors, heavy metal levels, and thyroid hormone levels. The data was organized in Excel spreadsheets, and analyzed using the SPSS program. After statistical analysis using Pearson correlations and multiple linear regression, the results recorded indicated that negative significant relationships exist between both heavy metals and FT3, T3, and T4. Thus, it is possible that increased heavy metal exposure, causing increased heavy metal levels in the blood, decreases thyroid hormone production. Therefore, increased heavy metal exposure may be a factor in the etiology of hypothyroidism diseases such as Hashimoto’s Thyroiditis.

Introduction

Heavy metal levels in the blood are very important for overall human health, and awareness of metals such as mercury (Hg) and lead (Pb) exposure has risen recently. People have become more conscious of exposure to lead via industrial environments and construction material and exposure to Hg in seafood. Such awareness is important because of the various harmful effects of high levels of heavy metals in the blood.

Because Hg occurs naturally in the environment, very low levels of Hg in air, water, and food are the primary sources of human exposure. Nevertheless, the amount of Hg that exists in the air, surface water, and soil are far below the levels considered unsafe to breath, drink, and be exposed to. Other sources of Hg exposure include dental enamel fillings, certain household products and industrial items (thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure devices), waste sites, certain medicinal products that contain mercurous chloride (laxatives, worming medications, and teething powders), and various working environments (manufacturing, electrical, construction, medical). One of the most common sources of exposure is diet, specifically certain fish, shellfish, or marine mammals that are from Hg-contaminated waters. Such foods contain methylmercury, which accumulates in the food chain, causing some fish to contain higher levels than others. According to the Food and Drug Administration (FDA), most people are exposed, on average, to about 50 ng of mercury per kilogram of body weight per day (50 ng/kg/day) in the food they eat. For adults of average weight, this amounts to approximately 3.5 μg of mercury per day. However, for the most part, this amount of exposure is not harmful. The FDA established an “action level” of 1 ppm for commercial fish involved in interstate commerce. Particularly, fish from local waters and other wild game are the most likely to have high levels of Hg. Also, some mushrooms that grow is Hg-contaminated soil have been found to be harmful if eaten in large quantities [13].

The body removes Hg from itself in different ways and with different efficiency based on the type of exposure. Inhalation of Hg vapors causes the body to absorb nearly 80% of the vapors into the bloodstream. This Hg then enters the brain and kidneys where is either remains as metallic Hg or can be converted into inorganic Hg, which may take several weeks or months to be excreted via urine and feces [13]. Thus, workers exposed to Hg in working environments where Hg vapors are prevalent can hold onto that Hg in their bodies from long periods of time. After you eat fish or other foods that are contaminated with methylmercury, about 95% of the consumed methylmercury enters your bloodstream easily and goes rapidly to other parts of your body. The methylmercury can easily be converted to inorganic Hg once in the bloodstream, which then can cause it to remain in the body for long periods of time [13].

The healthy amount of Hg in the blood is below 9.0 ng/mL [1]. However, a large amount of the general population have blood Hg levels above the healthy range. Increased mercury in the blood often causes impaired neurological development, especially in developing fetuses. In addition, mercury poisoning, caused by high levels of exposure, has been shown to hinder peripheral vision, weaken nervous responses, decrease coordination, weaken muscles, and impair speech, hearing, and walking. And, although not included in the EPA Cancer Guidelines in 2005, in limited data, Hg has been indicated to be potentially associated with tumor growth [2].

One of the most dramatic instances of Hg exposure took place in the Minamata area of Kyushu, Japan. In 1955 several cases of neurological disease were found in this region. It was discovered that these people had been exposed to very high levels of methylmercury from contaminated fish and shellfish in nearby waters. One year later the disease was called “Minamata Disease” In 1958, Professor Kitamura found that many infants from the region had symptoms similar to cerebral palsy. From 1959 to 1995, 1043 of the 2252 patients died. And, while this case was an extreme one, it demonstrates the extent of the toxicity that high Hg levels have on the human body.

Pb, like Hg, occurs naturally in the environment. However, most of the Pb that people are exposed to are the result of human activity, particularly leaded gasoline exhaust, mining, factories, and pesticides. This human activity leads to lead in the air, water, food, and soil. The environmental Pb rose dramatically between 1950 and 2000 primarily as a result of vehicle exhaust from leaded gasoline. Inhalation is often the greatest cause of Pb in the body, and burning leaded gasoline was at one point the primary source of Pb emissions. The EPA has taken steps to decrease the amount of Pb released into the environment by placing limitations and bans on leaded gasoline. Nevertheless, the inhalation of Pb, specifically by people working in metal (iron and steel) production factories, lead-acid-battery manufacturing, and nonferrous (brass and bronze) foundries, can cause harmful amounts of Pb to enter the body. Several other industrial workers are exposed to Pb regularly. Past uses of Pb have caused increases Pb levels in air, water and soil, which has also increased the levels of Pb in plants and animals from contaminated areas. Often the causes of Pb exposure for humans is exposure to hazardous waste sites, contaminated food or water, old houses that contain lead-based paint, pesticides, and jobs or hobbies that involve close-contact with lead products. Food accounts for a relatively small amount of exposure due to the regulations of packaging and food making. Drinking water supplies are also typically safe, but some can have acidic water, which makes it easy to increase Pb levels in the water from the lead piping [7].

Once this lead gets into a person’s lungs by inhalation, it goes quickly to other parts of the body via the blood. Most of the lead that enters the body comes from consumption. However, the amount of time since a person’s last meal is vital in determining the amount of Pb that the body absorbs into the blood. Typically, the sooner it has been since a person’s last meal, the body will absorb the less Pb. Shortly after lead gets into your body, it travels in the blood to soft tissues and organs. The Pb then moves primarily into bones and teeth, where it can find ways out of the body or may stay in the body for decades. Like Hg, most Pb is excreted via urine and feces. About 99% of the Pb taken into the body of an adult will leave in the waste within a couple of weeks, but only about 32% in children. Under conditions of continued exposure, not all of the lead that enters the body will be eliminated, and this may result in accumulation of lead in body tissues, especially bone [7].

The healthy range of Pb in the blood is any amount below 0.7 ng/mL. The typical diet in the United States contributes 1 ug to 3 ug of lead per day, of which 1% to 10% is absorbed [3]. Lead is extremely toxic, and exposure can cause interfere with hemoglobin synthesis, resulting in anemia and nervous system problems.

There have also been studies that indicate a relationship between Hg exposure and thyroid-related autoimmune responses. One study, in which a 13-year-old boy was exposed to Hg vapor for two weeks, resulted in the child’s triiodothyronine (T3) and thyroxine (T4) levels increasing drastically, while having a decrease in thyroid stimulating hormone (TSH) [4]. Another study showed slight, but significant, increase in free triiodothyronine (FT3) and free thyroxine (FT4) in industrial workers exposed to mercury vapor during their work over a 10 year period [5,6]. One explanation is the possibility of Hg increasing T4 and promoting the conversion of T4 into active T3 and FT3. However, two other occupational studies found no relationship between Hg exposure and endocrine function [11,12].

Blood Pb levels have also revealed relationships with thyroid hormones. Changes in levels of thyroid hormones, particularly T4 and TSH, have been shown to occur in exposed workers with blood Pb levels greater than 40-60 ug/dL [7]. However, several factors from previous studies such as subject exposure, subject age, subject tobacco use, and small sample sizes in those studies often caused inconsistent and inaccurate findings. In one study, T4 levels were found to decrease in workers with very high Pb [8]. Another study found that FT3 along with T4 were reduced when workers were exposed to occupational lead poisoning [9]. In yet another study, 93 workers with Pb ≤56 μg/dL and 83 workers with Pb ≥56 μg/dL were tested for thyroid hormone measures. Regression analysis found no significant correlations between Pb and any of the thyroid measures. However, there were weak but statistically significant negative correlations between duration of exposure and levels of T4 and FT4, and these associations were stronger in the ≥56 μg/dL subgroup [10].

Thus, the results of studies associating Pb and Hg levels to thyroid hormones are inconsistent, but tend to show some indication of significance in their relationship. This study’s goal was to minimize the known factors of blood Hg, blood Pb, and thyroid hormones, specifically diet. The study attempted to decrease the influence of diet by only using participants who claimed to be seafood consumers. In addition, all participants who were taking thyroid hormone supplements were removed from the study. Other variables were considered in recruitment and regression analysis such as age, gender, smoking, income, and ethnicity, along with other health-related information.

Materials and Methods:

*Recruitment and study population*

The parent study [19] recruited 290 adult, avid seafood consumers, defined as those predicted to be at risk for elevated Hg exposure due to regular fish consumption. Advertisements and in-person recruitment activities targeted for high fish consumers occurred at local fishing piers, seafood markets and restaurants, libraries, gyms, local newspapers, and on multiple university bulletin boards and websites. Participants were informed that they were being recruited for a study to investigate benefits and risks among avid seafood consumers. Participants completed an online screening survey that assessed their potential mercury exposure based on their responses to questions on the frequency and types of fish consumed, using seafood mercury concentrations from the parents study’s Seafood Hg Database [[1](#_ENREF_1)6] (Karimi et al., 2012). Individuals estimated to exceed the USEPA RfD of 0.1 g kg−1 day−1 were eligible to be in the study. This dose is designed to afford protection to sensitive populations over a lifetime of exposure, and translates to a blood total mercury (THg) level of 5.8 g L−1. In comparison, the European Tolerable Weekly Intake (TWI) [17] offers a less conservative corresponding blood total Hg concentration of 11.02 g L−1. However, recent studies suggest that the lower USEPA concentration may not afford adequate protection to the developing fetus [[18](#_ENREF_3)].

A total of 996 individuals completed the screening questionnaire, with the majority being eligible (n = 746). Of those deemed eligible, 290 participants enrolled in the study and completed a clinical appointment at the Clinical Research Core at Stony Brook University Medical Center. At the appointment, trained nurses obtained written informed consent and collected questionnaires, morphometric data, and blood specimens.

Demographic and information about health and lifestyle were obtained with a self-administered questionnaire. Some of the information obtained included age, gender, country of birth, race/ethnicity, annual household income, whether or not the subject smokes tobacco, diagnosis of medical conditions such as diabetes and thyroid disease, sleep hours, and indicators of mercury exposure. Those participants who were taking medications that alter thyroid hormone levels were dismissed from the statistical analysis.

*Blood metal collection and analysis*

The parent study [19] collected whole blood samples for trace metals analysis from 285 participants. Samples for the remaining five participants were not obtained due to complications with blood draw. Total Hg (THg) in whole blood is often used to determine exposure to methylmercury because nearly all of mercury in blood is in the methylated form particularly for the fish consuming population (and can be directly compared to the USEPA reference blood THg concentration (5.8 g L−1). Trained nurses collected whole blood specimens for blood metal analysis in BD trace element blood collection tubes.

Blood specimens were stored at 4◦C and sent to RTI International’s Trace Inorganics Laboratory (Research Triangle Park, NC) for analysis. Blood metal concentrations were analyzed using ICP-MS (Thermo X-Series II). A 1000 g mL−1Au solution (High Purity Standards) was added to each sample to stabilize the mercury. Samples were microwave digested with HNO3 and H2O2 (J.T. Baker, UltrexGrade), and diluted with deionized water prior to analysis. We digested and analyzed standard reference materials for external quality control, including NIST SRM955c caprine blood, NIST SRM966 bovine blood and UTAK human blood. The average percent recovery of standard reference materials was 110 ± 14% (n = 9). For each batch of approximately 100 samples, 2 sample blanks and at least 4 method blank samples were prepared to assess Hg and Pb background due to the sample collection method and the digestion method, respectively. A method blank and one mid-level calibration standard were analyzed every 10 samples throughout the analysis. All blood metal concentrations for sample blanks and method blanks were negligible, confirming no background contamination. Thus, blank corrections did not affect sample concentrations. Detection limits ranged from 0.10 to 0.70 µg THg L blood−1 and 0.02 to 0.50 µg Pb L blood-1 among sample batches. Samples that were below the detection limit (n = 2 for Hg) were assigned a value of one-half the detection limit for that batch.

*Thyroid hormone collection and analysis*

 Testing for thyroid hormones was done at the ARUP labs, a national laboratory for high throughput clinical tests. The tests looked at blood specimens for triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4), free thyroxine (FT4), and thyroid stimulating hormone (TSH). The tests were done on blood specimens from 294 subjects. However, some subjects’ thyroid hormone levels were discarded. In the statistical analysis, several subjects were also discarded due to the use of thyroid hormone supplements and/or inaccurate data. After certain subjects were discarded by the original data collection and by the analysis procedure, the resulting subject total was 258.

*Statistical Analysis*

Descriptive statistics including mean, standard deviation, and sample size were used to characterize the socio-demographic parameters, blood metal levels, and thyroid hormone levels of the sample. In addition, the data was stratified by age, gender, race/ethnicity, and household income for further statistical analysis. A Student T test was used to identify differences in the mean values of demographics, blood metals, and thyroid hormones within the categories. Because of their skewed distribution, in order to properly perform a regression analysis and Pearson’s Correlation test the blood metal and thyroid hormone levels were log-transformed.

 Bivariate correlations were performed to test the relationships between the blood metal levels, thyroid hormones, and the possible confounders. Multiple linear regression models were used to test relationships between the trace metals and thyroid hormone levels, adjusted for confounders. The regression models were adjusted for age, gender, race/ethnicity, household income, and highest education level. The confounders were determined by elimination via stepwise regression models and by retaining those inherently and previously associated with thyroid hormones and/or trace metals.

All statistical testing was performed in IBM SPSS Statistics 21. The criterion for significance was p<0.05.

Results and Discussion

*The Effects of Demographics on Heavy Metal and Thyroid Hormone Levels*

The study was conducted on 290 primarily white/Caucasian participants between 18 and 90 years of age. Thirty-seven participants that had insufficient data or were taking thyroid hormone supplements were eliminated from the sample. The resulting population of 257 participants contained 116 males and 142 females with an average age of approximately 47 years ± 18 years. The population had a wide variety of income levels and previous educations. Seventy-two percent of the participants had household incomes between $25,000 and $200,000 annually and 67% were college graduates.

 We found that age has significant relationships with Hg levels (r=0.301, p<0.001), Pb levels (r=0.551, p<0.001), FT3 (r=-0.367, p<0.001), T3 (r=-0.279, p<0.001), FT4 (r=0.128, p=0.041), and T4 (r=-0.228, p<0.001). Blood mercury and lead are known to increase with age [7]. In Robin P. Peters’ review article “Thyroid hormones and aging”, it was indicated that TSH along with FT3 typically decline with age due to the reduction of TSH secretion. This article also indicated that free and total T4 do not tend to be affected by age, while total serum T3 increases with age [20]. The data collected in this study contrast those finding with regard to T3 and FT4; however, the correlation with FT4 was the weakest of the significant correlations found with age.

 Gender was shown to have a significant relationship with Hg (x̄male=8.753, x̄female=6.683, p=0.043), FT3 (x̄male=3.200, x̄female=2.978, p<0.001), and T4 (x̄male=6.773, x̄female=7.438, p<0.001). According to one study conducted on nearly 300 residents of the St. Lawrence area of Quebec, men tended to have greater Hg levels than females [21]. However; Hg levels are often skewed based on diet, so the accuracy of such data is often unknown. This study analyzed only fish consuming participants, so, despite the varying amounts fish consumed, the influence of diet is relatively controlled. Like the aforementioned study, the present study found men having significantly greater Hg levels. Few previous studies regarding the relationship between gender and thyroid hormones exist, and those that do exist are inconsistent in their results. Due to the procedures taken to narrow the variations in thyroid hormone levels as a result of environmental factors and medications, we believe this study may provide a more accurate correlation, indicating that males have significantly greater FT3 levels and females have significantly greater T4 levels.

*Insert Table #1*

*Insert Table #2*

*Insert Table #3*

*Insert Table #4*

*Relationship of Heavy Metals and Thyroid Hormones*

 Pearson correlations indicated a significant relationship between Hg and FT3 (r=-0.144, p=0.021). In addition, Pb was shown to have significant relationships with FT3 (r=-0.264, p<0.001), T3 (r=-0.235, p<0.001), and T4 (r=-0.194, p=0.002). According to one previous study, TSH increased with Hg while it decreased with Pb. The same study did not find associations between the metals and T3 or T4 [22}. This study differed in that FT3 decreased with both Hg and Pb, T3 and T4 decreased with Pb, and TSH did not show any significant relationship with either metal.

 Multiple linear regressions indicated significant relationships between the metals and the thyroid hormones when adjusted for education, age, gender, race/ethnicity, and income. The results of had significant relationships with FT3, T3, and T4. This data shows that despite Pearson correlation results, all three heavy metals showed direct relationships with FT3, T3, and T4, when adjusted for age, gender, education levels, race/ethnicity, and income.

*Insert Tables #5-9*

Conclusion:

 This study found connections between Hg and FT3 and between Pb and FT3, T3, and T4. All of these significant correlations were negative, indicating that increased heavy metals in the blood are likely to decrease thyroid hormone production. Along with genetic functioning, environmental factors have been hypothesized to be influential in thyroid hormone production. And, several environmental factors, including heavy metals, have been linked to thyroid hormone production. This study offers an additional indication that heavy metals are correlated to thyroid hormone levels. Limitations existed in the study because the participants were not characterized by all the possible factors that influence heavy metal exposure. Therefore, in order to increase data accuracy, future research should attempt to include sources of Hg and Pb exposure on a broader scale in order to adjust the significance values for influential factors. In addition, the Pb levels calculated may not have been as accurate as possible due to the calibrations of the equipment which were set primarily to calculate Hg levels.

 Because this study supported the negative correlation between the heavy metals and the thyroid hormones, future research should continue studying the content of this study in order to continue increasing research accuracy by taking into account additional environmental and biological factors that influence heavy metals and thyroid hormones. Moreover, this study did not look for correlations between the heavy metals and several important thyroid hormones such as thyroid peroxidase (TPO), the thyroid peroxidase antibody (TPOAb), and thyroglobulin (Tg). Tg is considered a vital hormone in the indication of potential autoimmune thyroid disease. Because of thyroid hormone calculations for this study, the aforementioned thyroid hormones were not accurately recorded and, therefore, not included in the study.

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