

CLINICAL STUDY

Dental amalgam implantation and thyroid autoimmunity

Kisakol G

Acibadem University Medical Faculty, Acibadem Bursa Hospital, Turkey. gurcank@hotmail.com

Abstract: *Objective:* Mercury was heavily studied as a factor in the autoimmune processes. We aimed to observe whether mercury of amalgam is associated with Hashimoto disease.

Background: 363 patients with Hashimoto's thyroiditis and 365 control subjects were included in to the study. Amalgam fillings were checked by the physician.

Methods: 363 (49.9 %) patients and 365 (50.1 %) healthy controls were included into the study. Hashimoto's thyroiditis was diagnosed with thyroid hormones, antithyroid antibody levels, and ultrasonographic findings. Control subjects were selected from patients with no known autoimmune diseases. They were controlled with ultrasonography, as well as antibody titers. None of them had Hashimoto's thyroiditis.

Results: Sex distribution of the study population was following: 319 (87.9 %) female, 44 (12.1 %) male in the patient group and 277 (75.9 %) male and 88 (24.1 %) female in healthy control subjects, respectively. Mean free T4 values for Hashimoto's thyroiditis and healthy control group were 15.30 ± 0.76 , 17.30 ± 0.96 pmol/L and mean TSH values for Hashimoto's thyroiditis and healthy control group were 9.29 ± 20.79 , 1.20 ± 0.32 uIU/ml. Frequency of dental amalgam implantation in patients with Hashimoto's thyroiditis was not statistically significantly different from healthy controls ($p=186$) ($t=-1.324$)

Conclusions: Some studies identified mercury of amalgam as responsible for autoimmune thyroiditis. We studied whether amalgam fillings are more frequent in Hashimoto's thyroiditis patients and whether it is a causative factor for Hashimoto's thyroiditis. Statistical analysis revealed that there is no relation of amalgam with Hashimoto's thyroiditis (Tab. 1, Ref. 34). Text in PDF www.elis.sk.

Key words: Hashimoto's thyroiditis; thyroiditis; autoimmune; amalgam; mercury.

The human body is constantly exposed to metals and metal containing compounds. Some are crucial in trace amounts for normal metabolic function, but some are toxic. The key factor for toxicity is time of exposure, cumulative concentration and genetic susceptibility (1). Dental amalgam filling which contains approximately 50% of mercury is accepted a major source of mercury exposure in general population (2,3). Studies performed with sheep and monkey have shown that substantial amount of amalgam released from insertion of dental amalgam fillings accumulates in the body (4, 5). It is estimated that 100 million of amalgam fillings are inserted annually in USA (6). Immune system is of special interest as a target for low dose inorganic mercury (3). Case reports of accidental mercury exposure have shown that mercury can induce autoimmune reactions and/or systemic immune deposits in some individuals especially prone to this (7, 8, 9). In rodent models it was clearly shown that mercury induced systemic autoimmunity is strongly dependent on genetic constitution (10). Studies in animal models susceptible to mercury proposed that potential mechanisms by which inorganic mercury induced autoimmunity are T cell dependent activation and induction of autoimmune conditions, implying lymphoproliferation, immunostimulation of antinuclear antibody and immune complex formation (11). Besides mercury, implantation of alloy contain-

ing silver as well as oral silver exposure induce autoimmunity in genetically sensitive mouse strains (12, 13, 14). Endocrine organs can be a target for an autoimmune attack, leading to organ specific autoimmune disease such as thyroid autoimmunity (15). For development of thyroid autoimmunity several factors are required; These are genetic predisposition linked mainly to antigens of HLA system, namely HLA B8, B15, B5, DR3, DR4 and environmental factors such as viral and bacterial factors, iodine intake and heavy metal exposure.

While many researchers claimed that amalgam fillings contribute to a series of illnesses, many others did not identify such association. Latter group states that most people with fillings have less than 5 micrograms per liter of urine. Nearly all practicing dentists have levels below 10 micrograms per liter, even though they are exposed to mercury vapor when placing or removing amalgam filings and typically have amalgams in their own teeth. Thus, even with that exposure, the maximum levels found in dentists are only slightly higher than those of their patients and are far below the levels known to effect health, even in a minor way (16).

In this study, we intended to determine any relation between dental amalgam implantation and autoimmunity in patients with Hashimoto's thyroiditis.

Tab. 1. Statistical analysis of dental amalgam fillings between thyroiditis patients and control subjects.

	Dental amalgam (+)	Dental amalgam (-)	p value
Hashimoto's thyroiditis	200 55.7 %	159 44.3 %	>0.05
Control	190 52.1 %	175 47.9 %	

Acibadem University Medical Faculty, Acibadem Bursa Hospital, Turkey

Address for correspondence: Kisakol G, Acibadem Bursa Hospital, Acibadem University Medical Faculty, Sumer Sk. No: 1 Nilufer, Bursa, Turkey. Phone: +905422629638, Fax: +902244532201

Subjects and methods

363 patients with Hashimoto's thyroiditis diagnosed in Endocrinology department of Acibadem Bursa Hospital according to thyroid hormone levels, antimicrobial, antitiroglobulin antibody serum levels, clinical and ultrasonography findings. 365 control subjects were included into the study. Control subjects were selected from patients admitted to hospital with nodular goiter diagnosis. They were controlled with ultrasonography, as well as antibody titers. None had Hashimoto's thyroiditis. Those with type I diabetes mellitus, pernicious anemia, Addison disease, autoimmune hepatitis, autoimmune rheumatological and autoimmune hematological diseases, chronic liver disease, chronic renal disease, malignancy, viral hepatitis, pregnancy were excluded from the study. Also patients who were treated with interleukine, interferon and amiodarone were excluded from the study. Cases over 18 years old were included into the study. Patients were examined by endocrinologists, and amalgam fillings were noted. The study was performed with the permission of local ethical committee. For non-parametric analysis chi-square test was used. Anova was used for multiple comparisons between blood group antigens. $p < 0.05$ was accepted statistically significant.

Results

363 (49.9 %) patients and 365 (50.1 %) healthy controls were included into the study. Sex distribution was following: 319 (87.9 %) female, 44 (12.1 %) male in patient group and 277 (75.9 %) male and 88 (24.1 %) female in healthy control subjects, respectively. Mean free T4 values for Hashimoto's thyroiditis and healthy control group were 15.30 ± 0.76 , 17.30 ± 0.96 pmol/L and mean TSH values for Hashimoto's thyroiditis and healthy control group were 9.29 ± 20.79 , 1.20 ± 0.32 uIU/ml. Frequency of dental amalgam implantation in patients with Hashimoto's thyroiditis is not statistically significantly different from healthy controls ($p = 186$) ($t = -1.324$) (Tab. 1). According to risk analysis (OR: 0.863) 95 % confidence interval (0.644–1.156) there is no high risk attributable to amalgam fillings.

Discussion

Hashimoto's thyroiditis is the most frequent organ specific autoimmune disorder (15). Infiltrating lymphocytes and T cell mediated cytotoxicity are involved in the pathogenesis of autoimmune thyroiditis (16). It is seen more commonly in females. Gender, iodine insufficiency, smoking and aging are known risk factors related with Hashimoto's thyroiditis.

Metals in general, and mercury in particular have long been known as immunosuppressive agents. Although mercury is known as immunosuppressant, it was also shown to be stimulant to cellular and humoral immune system and even was regarded as responsible for autoimmunity (13). Many immunological effects caused by implantation of the amalgam such as hyperimmunoglobulinemia, development of serum autoantibodies with a nucleolar pattern/anti fibrillar antibodies (ANoA/AFA), potentiation of mitogen induced lymphocyte proliferation and increased expression of

class II molecules are consistent with the known effects of mercuric chloride on immune system in genetically susceptible mice and rats (17, 18, 19). Alloy/amalgam implantation or directly amalgam including mercuric chloride in SJL mice has precipitated the presence of serum autoantibodies with a nucleolar pattern (ANoA) against fibrillar (20). Antifibrillar antibodies are of interest in the medicine due to in nearly half of the scleroderma patients, ANoA targeting the fibrillar was detected (21). ANoA/AFA have been elucidated from kidneys from mercury treated SJL mice with immune complex disease indicating pathogenic role of autoantibodies in this pathology (22). On the other hand long term exposure to mercury from dental amalgam has not been shown to have causative role in the production of anti-glomerular basement membrane antibodies (23).

The reduction of mercury specific response following amalgam removal has been published in patients with thyroid autoimmunity (24). Amalgam mercury significantly contributes to long term thyroid burden of mercury (25). Kawada et al showed 50 % reduction in Na-K-ATPase activity in the membranous preparations from dog thyroid gland by mercuric chloride in 10^{-7} M concentrations (26). Following intraperitoneal injection of mercury de novo synthesis of iodothyronins was significantly decreased in mice. This suggests mercury may cause coupling defect in the synthesis of iodothyronins. In male Brown Norway rats $HgCl_2$ leads to production of autoantibodies capable of binding thyroglobulin (27). Prochazkova, Sterzl et al reported that lymphocyte reactivity measured with MELISA indicating in vitro reactivity after the replacement of dental amalgam decreased significantly to inorganic mercury, silver, organic mercury and lead. (28)

According to WHO Environmental Health Criteria, the estimated average release of elemental mercury vapour from dental amalgams in the general population is between 3.8–21 jg/day, and its retention in the body is 3–17 jg/day. According to another FAO/WHO report, the maximum weekly mercury intake with food regarded as having no adverse effect on health, is 300 jg in the form of inorganic mercury compounds and 200 jg per week in the form of methyl mercury (29).

According to National Council Against Health Fraud position paper on amalgam filling there is no reason to remove amalgam fillings other than amalgam induced allergy and problems related with fillings (30). In a controlled study, it was shown that many symptoms attributed to amalgam mercury were alleviated both by placebo and mercury chelation therapy, so there is currently not enough evidence to support for the recommendation for removal of amalgam in autoimmune disorders (31).

With respect to the reduced lymphocyte responses, Mackert et al (32) showed no indication that amalgam affects the human immune system, and no association was found between the number of amalgam fillings in individuals and Henoch-Schönlein purpura and acute glomerulonephritis, which are all autoimmune diseases. Epidemiologic studies have shown that occupational exposure to mercury does not usually result in autoimmunity. Mercury does induce antinuclear antibodies, scleroderma-like diseases, lichen planus, or membranous nephropathy in some individuals, however, immunogenetic and pharmacogenetic factors are responsible

for the induction of metal-associated autoimmunity in general (33). In addition to estrogen replacement therapy, other factors including mercuric chloride are putative risk factors for the development of lupus, scleroderma, and Raynaud disease. Urinary mercury excretion has been reported to be higher in scleroderma patients who are positive for antifibrillar antibodies. However this level is still in the normal and unexposed ranges, and these patients never develop immune complex glomerulonephritis (34).

In our study, we did not observe any significant relation between amalgam and autoimmune thyroiditis, nor there was increased risk. Non-evaluation of fecal and urine silver and mercury levels that represents the release of these metals from amalgam implants was the limitation of present study however as mentioned previously urine excretion of mercury in amalgam patients is not over normal limits. In the light of some studies it may be assumed that mercury of amalgam might be responsible for autoimmune diseases. We did not study other possible side effects of mercury over immune system however according to our results mercury is not responsible for thyroid autoimmunity.

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Received February 27, 2012.

Accepted August 18, 2013.