

Diagnosis and treatment of metal-induced side-effects

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Submitted: December 2, 2006

Accepted: December 18, 2006

Key words: **autoimmunity; allergy; chronic fatigue syndrome; genetics; lymphocyte; LTT; MELISA®; patch test; metals; mercury; gold; titanium**

Neuroendocrinol Lett 2006; 27(Suppl 1):7-16 PMID: 17261999 NEL270706A09 © Neuroendocrinology Letters www.nel.edu

Abstract

Environmental factors are recognized as a cause of the increasing frequency of allergic and autoimmune diseases. In addition to external pollutants, metal ions released from dental restorations or from other body implants might trigger inflammation in susceptible subjects. In humans, genes governing metal-induced inflammation and autoimmunity are not yet known.

In clinical praxis, metal-sensitive patients will present various symptoms ranging from oral mucosal changes and skin disease to excessive fatigue and autoimmune diseases. Since genetic markers of genetic susceptibility in man are not known, one has to rely on the phenotypic markers. Such biomarkers might be certain detoxification enzymes but also the presence of metal-specific memory cells in the blood. With the increasing use of metal implants in medicine and dentistry, it is important to have a proper tool for the diagnosis of metal allergy in susceptible subjects.

In addition to patch test, an *in vitro* blood test, an optimized commercially available lymphocyte transformation test (MELISA®) is discussed. Both tests were used for the diagnosis of metal allergy in a selected group of 15 patients who suffered from clinical metal sensitivity in addition to other health problems. The concordance of the two tests was good but MELISA® detected more metal allergies than patch test. The removal of incompatible dental material (RID) resulted in long-term health improvement in the majority of patients. We postulate that *in vivo*, metal ions activate T-cells, initiating systemic inflammation, which, through cytokines, affects the brain and hypothalamus-pituitary-adrenal axis.

We postulate that *in vivo* metal ions will activate T-cells starting systemic inflammation which, through cytokines affect the brain and hypothalamus-pituitary-adrenal (HPA) axis.

The treatment and rehabilitation of metal sensitive patients is based on a firm understanding and recognition of individual susceptibility. RID has to be done with extreme caution and according to standard working protocol. If performed properly, this treatment can result in decreased systemic inflammation and improved health in sensitized patients.

To cite this article: Stejskal VD, Hudecek R, Stejskal J, Sterzl I. Diagnosis and treatment of metal-induced side-effects.

Neuro Endocrinol Lett 2006; 27 (Suppl 1): 7-16.

Abbreviations

CFS	– chronic fatigue syndrome
RID	– removal of incompatible dental material
SH	– sulfhydryl
GSTT1	– glutathione s transferase T1
GSTM1	– glutathione s transferase M1
SLS	– sodium lauryl sulfate
LTT	– lymphocyte transformation test
SI	– stimulation index
MRI	– magnetic resonance imaging
CNS	– central nervous system

Background

Mankind is exposed to toxic particles, such as metals, on a daily basis through contaminated food and air. Environmental toxins can be one of the etiological factors behind the increase of so-called modern illnesses: allergies, autoimmunity and cancer [14, 28, 33, 66, 67]. The role of the organic mercury (Hg) compound thimerosal as a factor contributing to the increased frequency of autistic disorders has also been widely discussed [16, 17, 42]. In addition, metal-based medical devices such as dental restorative materials (e. g. amalgam and gold alloys) release metal ions and contribute to internal pollution.

Dental restorative materials are developed for replacement of tooth substance which is lost and are placed in the teeth for long periods of time. Previously, the majority of such materials were based on various metal alloys, but in modern dentistry, the use of non-metallic dental materials, for example ceramics, is steadily increasing.

Such materials should preferably be free from toxic and/or allergenic substances which might affect the patients' and dental staffs' health. Special care has to be taken in patients with known allergy and/or autoimmunity.

Metals affect the immune system in several ways. In the oral cavity, a high concentration of metal ions may be toxic and act as a local immunosuppressant. This may explain why the oral mucosa contains only a low number of dendritic cells, and why mucosal changes adjacent to dental metal fillings are infrequent [35]. Nielsen and Klaschka [45] have shown that a 5–12 times higher concentration of the allergen has to be applied on the oral mucosa than on the skin to elicit microscopic reaction.

Certain metals stimulate the immune system non-specifically as shown by increased levels of serum immunoglobulins in workers professionally exposed to Hg [5]. Further, an abnormal antioxidant system with reduced levels of glutathione and catalase activity was found in Hg exposed workers [54]. In the general population, anti-oxidant capacity of serum is inversely related to the number of amalgam fillings, as described by Pizzichini and coworkers [49]. Interestingly, glutathione depletion inhibits TH1-associated cytokine production and/or favors TH2-associated responses [46]. This might explain the TH1 to TH2 switch in animals treated with low concentrations of inorganic Hg [19, 50]. In contrast, in

some hereditarily predisposed individuals, metals may act as specific allergens [6, 11, 21, 29, 37, 51].

The majority of metals used in dental alloys belongs to the group of transition metals in Mendeleev's periodic table. A general characteristic of these elements is the strong binding capacity to various groups of enzymes and cells in the body. Transition metals form strong complexes with both organic and inorganic ligands [85]. Metals bind to sulfhydryl (SH) and other groups, thus altering the molecular structure of autologous proteins. T-lymphocytes mistakenly recognize metal-modified cells as foreign and start the autoimmune process [20]. The term "allergy" was coined by von Pirquet to describe a deviant immunological reaction – hypersensitivity [48].

It has to be emphasized that metals are only one of several agents which may trigger chronic inflammation and thus significantly contribute to chronic fatigue syndrome (CFS) and autoimmune diseases. The role of other agents, such as microbial [79] or viral, in inflammatory processes is reviewed elsewhere [15].

Biomarkers of harmful effects of metals and other environmental pollutants include detoxification enzymes, such as apolipoprotein E, where the substitution of cysteine with arginine – an amino acid lacking SH-groups – predisposes for increased risk for Alzheimer's disease [18] and increases vulnerability to chronic mercury toxicity [91]. Other detoxification enzymes of importance are glutathione s transferase T1 (GSTT1) and glutathione s transferase M1 (GSTM1). As shown by Westphal's group [90], homozygous deletion of GSTT1 and combined deletion of GSTT1-/GSTM1- was markedly more frequent in patients sensitized by thimerosal, than in healthy controls.

Regarding metal susceptibility, measurement of beryllium (Be) specific memory cells in the blood of exposed workers is currently the golden standard for detection of Be-susceptibility [30, 31, 44]. Since clinical reactions to metals, such as local skin reactions or systemic reactions (fever, profound fatigue, multiple chemical sensitivity) are not experienced by all exposed individuals, standard case-control studies with a small number of participants, who are not matched for the susceptible genotype, are of limited value [89]. Instead, a suitable cohort should consist of patients suffering from the same symptoms but selected on the basis of susceptible phenotype; for example, patients suffering from CFS and clinical metal sensitivity [52, 76, 78].

Thus, the best way to study the possible role of metals in the pathogenesis of diseases seems to be first, the selection of susceptible patients from a heterogeneous multi-factorial cohort; second, therapy based on the elimination of the exposure to putative allergen(s); and third, long-term follow-up of patient's health. Finally, it is also important to bear in mind that exposure to metals can originate from all types of metal-containing medical devices, and not only from dental appliances. Other

sources are foods [55], jewelry, cosmetics, vaccines, metallic razors [12] and contaminated air (cigarette smoke, pollution).

T-lymphocytes are key players in inflammation and autoimmunity

T-lymphocytes play a key role in all types of allergic and autoimmune reactions [19, 20, 56]. After contact with an allergen, allergen-specific T-lymphocytes, together with B-cells and macrophages, are activated and inflammation may occur locally or in other parts of the body. The allergen specificity is retained on the surface of memory cells. Memory lymphocytes (Fig. 1a) circulate in the blood and the lymph, which explains why allergy is a systemic phenomenon. Exposure to the same or chemically similar (cross-reacting) substance will induce a faster, secondary reaction. Cytokine release by activated lymphocytes and macrophages will result in deregulation of the hypothalamus-pituitary-adrenal axis, as well as in multi-systemic symptoms such as profound fatigue, psychosomatic problems and sleep disturbances [9, 39, 65, 68, 84].

In vivo testing

Currently, the patch test is the only test available for routine *in vivo* diagnosis of delayed type hypersensitivity. Although the test is useful in clinical praxis, it has several disadvantages [36, 43, 66, 87]. Direct application of the allergen under occlusion on the skin might boost already existing sensitivity, which might aggravate patients' symptoms [36]. Some allergens, such as gold (Au) salts, may carry the risk of sensitization [43, 58] and positive patch test reactions may persist for months. Patch test results can also be affected by the condition of the skin; fair-haired patients usually have more sensitive skin. In pre-menopausal women, the patch test results may vary depending on the menstrual cycle [80]. Under standard conditions, only 7% out of the total amount of nickel (Ni) applied will penetrate the skin [13]. If the permeability of the skin is increased by local pretreatment by a surfactant such as sodium lauryl sulfate (SLS), the penetration of metals through the skin increases, which improves the accuracy of patch testing [62]. SLS might be beneficial in patch testing but its presence as an ingredient in toothpaste, soap and shampoo should be questioned.

In spite of the fact that the patch test is regarded as golden standard, the test, as such, is for many allergens not standardized. Allergens can be diluted in water or applied in undiluted form in petrolatum.

Finally, the evaluation of patch testing is subjective and depends on the skills of the evaluating specialist. The results of patch testing with skin-irritating substances such as Hg salts or formaldehyde may be unreliable since toxic reactions due to irritation are difficult to discriminate from allergic reactions [12].

In vitro testing

The lymphocyte transformation test (LTT) uses the property of memory cells to be re-stimulated by a specific allergen. Lymphocytes are isolated from peripheral blood on a density gradient and cultivated with metal salts for 5 days in 37°C. If memory cells are present in the blood, they start to divide and differentiate to so-called lymphoblasts (Fig. 1a). Proliferation is measured by the uptake of radiolabeled thymidine into newly synthesized DNA. The proliferation in metal-treated cultures is compared with cells incubated in the absence of metal salts and expressed as an Stimulation Index (SI). $SI = \text{counts per minute in metal-treated cultures} / \text{counts per minute in control cultures}$. $SI \geq 3$ is considered as a positive response while $SI 2-3$ is considered a weakly positive response [73, 74].

In the case of low molecular substances, allergen-specific memory cells are found in the blood of subjects experiencing exposure-related clinical symptoms but not in the majority of healthy non-allergic subjects [30, 60, 64, 69-74, 76, 77].

Memory cells can be detected in the blood of sensitized individuals already prior to the appearance of visible clinical reactions. Thus, workers with Be-specific *in vitro* lymphocyte responses have been diagnosed as Be-allergic even if the symptoms of the chronic lung disease berylliosis were not yet apparent [30, 31, 44]. Following the relocation to a Be-free environment, these workers did not develop berylliosis and remained healthy.

For decades, it has been known that inorganic Hg salt ($HgCl_2$) activated human lymphocytes *in vitro* regardless of the donor's Hg allergy status [8, 61]. Hence, to be able to use LTT for diagnosis of Hg allergy, it was necessary to modify the test in such a way that only lymphocytes from patients with Hg-induced symptoms were activated [74]. This was achieved by reducing the concentrations of Hg salts added to cultures to suboptimal concentrations (0.5 µg per 1 ml culture) [73, 74]. The same turned out to be true for Ni [59, 60, 64] as well as Au and palladium (Pd) salts, where a concentration of 5 µg per culture is routinely used [73]. This modified LTT was named MELISA®, an acronym for Memory Lymphocyte Immuno Stimulation Assay [73]. Another important modification was the increase of the total number of lymphocytes to 1×10^6 cells instead of 2×10^5 cells used in standard LTT. The key importance of lymphocyte concentration for optimal results has been described by Valentine-Thon [86]. Further, since the number of monocytes (Fig. 1b) increased during the preparation procedure, it was necessary to bring the amount of monocytes back to the normal value by partial monocyte depletion. Although necessary for antigen presentation to T-cells, activated monocytes produce prostaglandins [27] which negatively affect lymphocyte activation [57].

At Astra Pharmaceuticals, the MELISA® test was originally used for the diagnosis of occupational allergy to drugs in the pharmaceutical industry [69, 70]. Later

Table 1. The results of patch test and MELISA® in 15 patients with clinical metal sensitivity and temporary worsening of symptoms in connection with dental treatment (2–3 days later).

Pat. nr	Sex	Age (years)	Clinical symptoms	Dental metal exposure	Patch test ⁱ	MELISA® Stimulation Index (SI)	Therapy	Clinical effect of therapy
BE	M	48	CFS, sinusitis, dry eyes, joint pain	17 AF ⁱⁱ 1 Au crown 5 RF ⁱⁱⁱ 1 gold-plated pin	Au ++ ^{iv} PhHg - Hg -	Au ++ (15) PhHg + (3.3) Hg ± (2.9)	Removal of all metals 1 RF with Au pin left	1 yr later: much better, joint pain gone, eye dryness decreased. Sinusitis persists.
EH	F	48	Crohn's disease, abnormal fatigue, oral problems	AF in all teeth MBP ^v Au crowns 10 RF (brass pins)	Au ± Pd -	Au + (10) Pd + (3.3)	1. AF replaced with Au crowns 2. Au replaced to ceramic crowns, RF with brass pins replaced	1. Worsening of health. 2. Health improvement. Decrease in lymphocyte responses to Au (SI 2.7)
GCH	M	53	Urticaria on the back after dental treatment eczema, acne, psychiatric problems, anxiety, depression	25 AF 2 Au restorations brass pin on AF crown 2 RF	Au + Hg -	Au ++ (10) Hg - (1.4)	Replacement of all metals	2 yrs after replacement: decreased skin problems and psychiatric symptoms.
AS	F	45	Neurological symptoms and eczema after insertion of MBP	10 AF 6 MBP crowns RF with AF & Au pin	Ni + Au - Pd - Cu +	Ni ++ (37) Au ++ (11) Pd ++ (10.2) Cu - (1)	Removal of most metals 9 AF left	2 yrs after replacement: some symptoms disappeared and some became worse.
IH	F	62	Polymyalgia rheumatica following replacement of AF with Au crowns and bridges	AF (previously) Au crowns 5 RF with screws	Ni + Au + PhHg - Pd - Hg -	Ni + (9.7) Au ++ (19) PhHg ± (2.7) Pd ± (2.6) Hg - (0.9)	Removal of Au and RF, rests of AF found under the Au crowns	2 yrs after replacement: long term health improvement. Decrease in lymphocyte responses to Au (SI 2) and Ni (SI 4.2)
LL	F	44	CFS, fibromyalgia, oral symptoms, eczema, headache	13 AF 2 Au-plated brass screws in RF	Ni ++ Pd ± Hg - Al ± Au -	Ni+ (7.7) Pd ++ (18) Hg+ (4.9) Al - (1.9) Au- (1.6)	Removal of all metals including corroded screws in RF anti-oxidant therapy	1 yr later: partly better, still fatigued, back pain, muscle pain better. 2 yrs later: further health improvement
IB	F	41	Oral symptoms and eczema after insertion of Pd-containing bridge	AF (previously) Au bridge	Ni ++ Pd ± Au - Cr ++	Ni ++ (32) Pd + (9) Au + (3.6) Cr not done	Removal of Au bridge	2 yrs later: marked improvement in oral health
EV	F	52	Thyroiditis with autoantibodies, fatigue, endocrine problems	9 AF	Ni ++ Hg -	Ni ++ (43) Hg ++ (18.8) Sn + (3.5) MeHg + (5.8) PhHg + (6.5)	Removal of AF anti-oxidant therapy	2 yrs later: improved health and decrease of lymphocyte reactivity to Hg (SI 5), Ni (SI 11) and MeHg (SI 1.7). 9 yrs later: good health persists.
DF	F	39	CFS, joint pain, provocation with Hg positive	25 AF MBP Au crowns 3 RF	Hg - Au ± Ni -	Hg + (7) Au - (1.3) Ni - (1.1) PhHg + (5.6) Sn + (3.7)	Removal of all metals	Health improvement
CD	F	66	Oral symptoms after placement of Au bridge, fibromyalgia	AF MBP bridge containing Au, Pd and Ag	Au - Ni - Pd - Ag -	Au + (4.2) Ni + (4.4) Pd ± (1.7) Ag - (1.2)	Removal of all metals	No health improvement
BZ	F	64	Mucosal problems around metal prosthesis, gingivitis	AF (previously) Ti crowns RF with screws Metal prosthesis (Cr, Mo and 2% Ni)	Ni ++ Au ++ Pd ++	Ni ++ (15.5) Au + (3.7) Pd + (4.3)	Removal of metal prosthesis and RF	Improvement of oral health

Pat. nr	Sex	Age (years)	Clinical symptoms	Dental metal exposure	Patch test ⁱ	MELISA® Stimulation Index (SI)	Therapy	Clinical effect of therapy
JK	M	49	CFS, depression, facial eczema after dental treatment	6 AF 2 Au bridges 1 RF	Au + Ni - Hg - PhHg -	Au ++ (14) Ni ++ (27) Hg + (4.6) PhHg + (4.5)	Removal of all metals antioxidant therapy	2 yrs later: successive health improvement
BBR	F	46	Optical neuritis, multiple sclerosis, asthma, known nickel allergy	16 AF	Hg ++ Ni -	Hg + (5.6) Ni + (6.3)	Removal of all metals anti-oxidant therapy	Symptom free for 15 yrs, MRI is normal. Lymphocyte reaction to Hg -
AD	M	46	Optical neuritis and multiple sclerosis, joint pain	AF (previously) Au crowns 1 MBP RF containing N ₂ (PhHg)	Au + PhenylHg - Hg -	Au + (3.9) PhenylHg + (3.5) Hg - (1.3)	1. AF replaced with MBP 2. MBP replaced with ceramic material RF filling extracted Anti-oxidant therapy	1. Worsening of health. 2. Improvement of health, no relapse in multiple sclerosis for 15 yrs. Decrease in Au responses <i>in vitro</i> .
BML	F	49	Sjögren's syndrome, electrosensitivity, Hashimoto thyroiditis,	AF (previously) 4 RF with Au pins MBP	Au - Pd not done Ni +	Au + (7) Pd + (5.5) Ni ++ (11.9)	Removal of all metals pins in RF were corroded	1 yrs later: health improvement, electrosensitivity disappeared. 3 yrs later: lymphocyte reactivity decreased to Au (SI 3.2) and Pd (SI 3.2)

i) Test done according to Marcusson [35,71]; ii) Amalgam fillings; iii) Root fillings.

iv) + positive reaction, ± weakly positive, - negative reaction;

v) Metal-bound porcelain

on, the test was developed for detection of cell-mediated immune responses to formaldehyde [69], industrial epoxides [69], Kathon CG [71], mercurials [73, 74, 76], as well as for other metals [73, 75, 76]. In addition to type 4 allergy, the test has also been used for the diagnosis of immediate hypersensitivity (type 1 allergy) due to psyllium exposure in geriatric wards [72]. It can also be used for the monitoring of desensitization to insect venoms (unpublished). Recently, the value of LTT in the diagnosis of drug allergy has been reviewed by Pichler and Tilch [47], and for the measurement of Ni allergy by Sanchez and colleagues [60].

Comparison of patch test with MELISA® test

Clinically, patients with intolerance to dental materials often display multiple metal allergies which can be demonstrated by patch test or by MELISA®. From a larger group of patients monitored by us for several years, 15 are described in detail in Table 1. In addition to inorganic Hg, reactivity to Au, Pd and Ni was often present. Patch test results and *in vitro* lymphocyte responses were usually in accord. However, in some patients, patch test was negative despite of positive MELISA® test. The limited value of patch test for diagnosis of Hg

allergy has been reported elsewhere [66]. In the majority of patients, replacement of metallic appliances with ceramic and composite materials resulted in long-term health improvement. This is in agreement with previous publications [51, 76, 77, 87, 92]. Together with improved health, lymphocyte responses to dental metals also decreased after RID, reflecting the down-regulation of inflammation *in vivo*.

Undesirable effects of dental materials

Regarding side-effects caused by dental materials, the focus has until now been primarily on local oral problems (Fig. 2). This is despite of the fact that already in 1982, Swedish researchers described that "allergens released in the mouth may result in allergic reactions in other parts of the body, or worsen or maintain such reactions without any local reaction in the oral mucosa" [35]. Only a few reports describe reactions in other parts of the body. For example, Hay [22] describes a case of recurring facial dermatitis after dental treatment. The patient had facial symptoms as well as lichenoid reactions near the dental amalgam; the same reactions were induced by dental gold. The patch test showed a strong reaction to cobalt (Co), Ni, copper (Cu), and Pd – and a

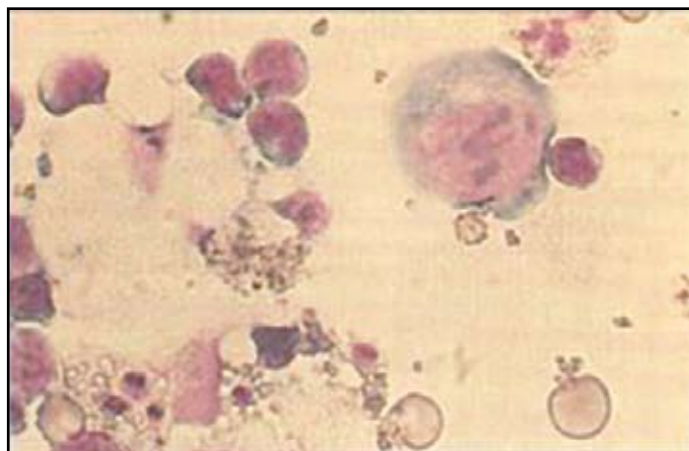


Figure 1a. One large stimulated lymphoblast and small, non-stimulated lymphocytes.

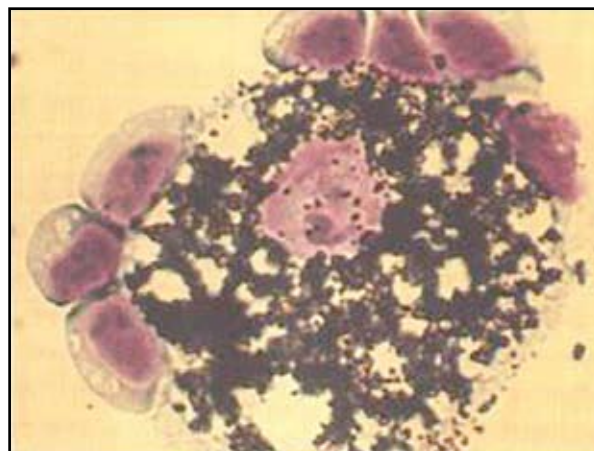


Figure 1b. Macrophage containing titanium dioxide, surrounded by small lymphocytes.

weak reaction to inorganic Hg and Au thiosulphate. The tests were negative to all other materials tested, including latex and acrylic materials (methyl-hydroquinone).

Laine and co-workers in Finland [32] studied allergy to different restorative materials in 118 patients with oral lichenoid changes adjacent to metal fillings. The contact allergy was determined by patch testing. Eighty patients (68%) showed positive results. Seventy-six patients (64%) were reactive to Hg, 11 (9%) to Au, 4 (3%) to Co, and 2.5% reacted to tin (Sn), silver (Ag), or Pd. Allergic reactions to acrylates, a composite component, was not detected. Removal of metal fillings was performed in 62 out of 80 patch test-positive patients and healing of the oral mucosa was observed in almost 50% of the cases. The authors point out that allergy to acrylates may be caused by negligent use of non-hardened acrylate monomers during dental work, but it is not a problem following hardening in oral cavity.

Metallic Au used in dental alloys has previously been regarded as inert and Au-induced contact allergy as a rare phenomenon. This changed when Björkner and co-workers reported that 8.6% of patients referred to the Dermatology Clinics in Malmö, Sweden, reacted positively to Au thiosulfate in patch test [6]. This was later confirmed by Marcusson [37] who tested 397 patients with multi-symptoms suspected to be caused by dental restorative metals. The frequency of patch test-positive patients was 23% for Au, 8% for Pd, and 4% for inorganic Hg and ethyl Hg. In contrast, a study of 2,853 patients in Portugal demonstrated that only 0.8% of the patients – all women – suffered from Au allergy [63]. The authors speculate that the reason for the low frequency of Au allergy is that golden alloys are rarely used in dentistry in Portugal. Swedish researchers [1, 2] further reported that Au-positive patch test correlated with the number of patients' Au restorations, and that the concentration of Au in saliva and serum correlated with the number of Au restorations as well. These findings corroborate the original findings of Drasch and co-workers [10] regard-

ing correlation of Au and Pd in the saliva with the number of Au restorations. Hence, the aggressive environment in the oral cavity, including oral bacteria and acidic pH, as well as the presence of galvanic streams among disparate metals [41, 53, 88] may contribute to increased corrosion and to a higher frequency of Au sensitization.

Titanium allergy: does it exist?

Titanium (Ti) is increasingly used in dental and body implants. It is rapidly oxidized to titanium dioxide, TiO_2 , a white coloring agent added to drugs, candy, food, cosmetics, sunscreen, toothpaste and chewing gum [75]. The reactivity of Ti with oxygen is due to its physiochemical properties as a transition element and this reactivity is greatly enhanced by the presence of fluoride ions [83]. Protein reactivity together with the ability to trigger free radicals [23, 81] should be of concern when evaluating the possible adverse effects of Ti in humans.

In dermatology, the allergenic potential of Ti is virtually unknown since patch test invariably turns negative [24, 40]. This could be due to the fact that testing is performed with a suspension of TiO_2 which has only limited diffusion through the skin.

In 650 Swedish patients with clinically verified or suspected metal hypersensitivity, 3% were positive to TiO_2 in MELISA® testing [75]. Valentine-Thon and colleagues [87] found similar results among 700 patients in northern Germany, where 4.2% reacted to TiO_2 . Finally, Müller et al. [40] reported on 56 patients who developed health problems after receiving Ti-based implants. In the MELISA® test, more than half responded with increased proliferation to Ti, although they were all patch test negative. In patients who did not respond to Ti *in vitro*, a majority responded to other metals. Clinical symptoms disappeared or improved dramatically after implant replacement.

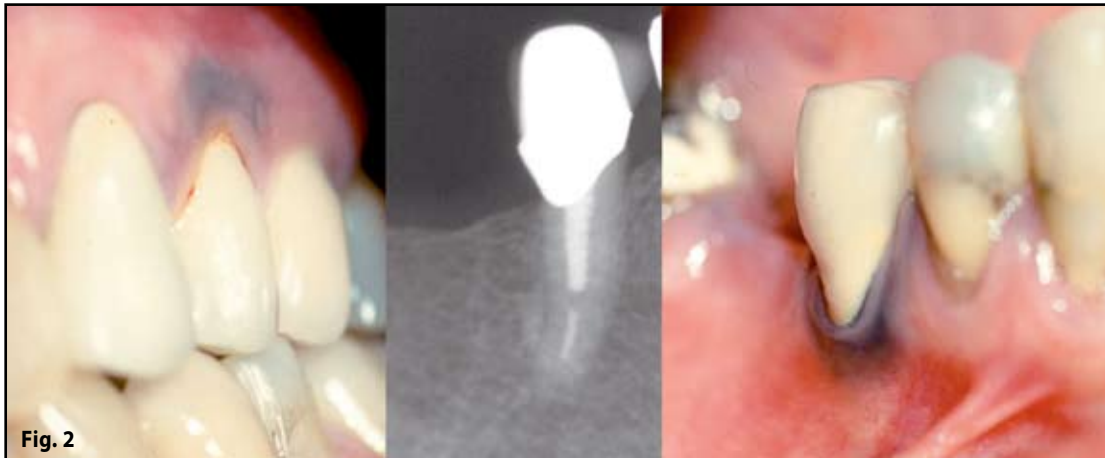


Fig. 2

Figure 2. Metal-ceramic crowns on teeth 24 and 45. In the roots of these teeth Ti posts have been placed (centre). Observe the changes in the adjacent mucosa (black coloration of the gingiva) due to corrosion products of metals.

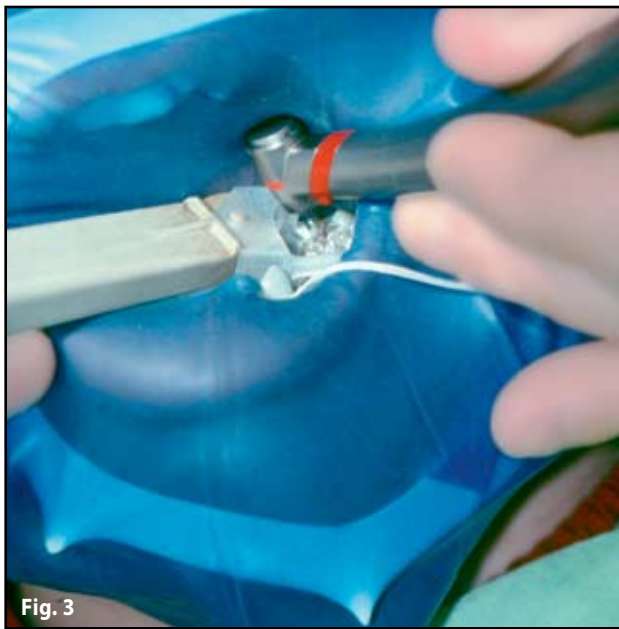


Fig. 3

Figure 3. Rubber-dam and Clean-up® applied during amalgam removal.

***In vitro* responses in patients and controls**

The frequency of metal-induced lymphocyte responses was examined in 3,162 patients in three European laboratories (two Swedish and one German) using MELISA® [76]. Patients suffered from oral symptoms such as oral lichen planus, burning and itching and systemic symptoms resembling CFS. In both countries, the most frequent metal allergen found was Ni, followed by inorganic Hg, Au, phenyl Hg, Pd, cadmium and Ti. Positive responses to other metals such as Ag, platinum (Pt) and Cu were only rarely observed. Similar results were later published by others who also validated the MELISA® method [86, 87].

Sterzl et al. [77] reported that lymphocytes from fatigued patients suffering from autoimmune thyroiditis responded more frequently to Ni and inorganic Hg than healthy controls. The increased Ni allergy in CFS patients was also demonstrated by patch testing [37, 38]. Regland et al. [55] have shown that female patients with Ni allergy suffering from fibromyalgia will improve on a low Ni-diet.

Tibbling et al. [82] used magnetic resonance imaging (MRI) to examine 32 patients with central nervous system (CNS) and systemic multi-symptoms suggestive of metal-induced pathology. Metal responsiveness at the lymphocyte level was examined by MELISA® and lymphocyte phenotype was analyzed with flow cytometry. One hundred twenty age-matched patients without CNS symptoms served as controls for the MRI study, 77 healthy subjects with dental amalgam fillings served as controls for MELISA® and 75 served as controls for phenotype determination. Pathological MRI findings were present in 81% of the patients, most of them with signs of degeneration in the basal ganglia, but none was found in the controls. The MELISA® test showed a higher frequency of metal-specific responses in patients than in controls. The difference in metal reactivity was highly significant for inorganic Hg ($p < 0.001$), phenyl Hg ($p < 0.002$), and Au ($p < 0.005$), weakly significant for lead ($p = 0.05$) and not significant for the remaining metals. In both patients and controls, Ni was the most frequent allergen. The lymphocyte phenotype determination was pathological in 58% of patients. Sixty-two of the patients

had atopic diseases and 35% suffered from hypothyroidism. The authors concluded that dental restorative metals may play an important role in the development of the brain lesions in patients with basal ganglia disorders.

The impact of RID

Anneroth and co-workers [3] studied 10 patients who suspected amalgam replacement as a cause of aggravation of their symptoms. Six of 10 patients had contact allergies due to metals; three of them were induced by inorganic Hg. The changes in laboratory tests prior and after amalgam removal indicated that amalgam drilling might have activated the immune system.

The effect of dental metal replacement with metal-free restorations was studied in 111 CFS patients with metal allergy [76]. Following RID, 83 patients (73%) reported long-term health improvement. Twenty-four patients (22%) reported unchanged health and two (2%) reported worsening of symptoms. There was a marked decrease in lymphocyte reactivity to inorganic Hg as well as to other metals used as components or dental alloys. These data have been confirmed in larger studies [34, 92].

Prochazkova and coworkers [52] were first to show that amalgam removal in Hg-sensitive patients suffering from various autoimmune diseases, such as multiple sclerosis or rheumatoid arthritis, resulted in down-regulation of Hg-specific responses *in vitro* and long-term health improvement. This also correlated with the decrease of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies [78]. In contrast, Hg-sensitive patients who refrained from amalgam replacement did not show any health changes half a year later. In this group, the level of autoantibodies and lymphocyte responsiveness to inorganic Hg *in vitro* remained the same as at the start of study. The authors conclude that removal of dental amalgam in patients with Hg-sensitivity might contribute to successful treatment of autoimmune diseases.

The following case illustrates the importance of proper diagnosis and dental treatment for the rehabilitation of a patient. A female nurse suffered from electrosensitivity, fatigue, depression, and social phobia. She had on several occasions been exposed to broken Hg-containing thermometers, and suspected dental amalgam as the cause of her ill health. Amalgam was replaced with a white Au bridge but health problems persisted. Analysis of the cerebrospinal fluid showed a negligible amount of Hg (0,6 µg/l, reference range <1 µg/l), but a high concentration of Pt (5 µg/l), a component of the bridge. The patient's lymphocytes reacted positively *in vitro* to Pt (SI=5,4), Pd (SI=5,3) and weakly to Sn (SI=2,8). Lymphocyte responses were negative to thimerosal, Ti, Ag, Cu, Au, methyl Hg, phenyl Hg and inorganic Hg. Since Pd, Sn and Pt were components of her white Au bridge, it was replaced with a ceramic bridge. The patient's fatigue, electrosensitivity, depression and social phobia diminished and 10 years on she still enjoys good health.

The dentist's role in the treatment of patients with clinical metal allergy is of utmost importance. All mechanical work in the oral cavity may result in increased exposure to potentially allergenic substances and consequently to temporary worsening of patient's symptoms (Table 1). By strict use of precautionary measures and safety devices it is possible to reduce the exposure to a level where serious side-effects are rare and only occur in particularly sensitive patients.

Precautionary measures during RID is the use of rubber-dam, Clean-up® (CleanDent, Sweden) (Fig. 3), traps that remove Hg vapor from the air, and fresh-air outlets. The choice of instruments, such as the type of drill, drilling speed and the use of manual instruments for removal of fillings, has been described in detail previously [25, 26].

In addition to ceramics and composites, zirconia holds the promise of one of the future's immuno-compatible implant materials [7]. Finally, a patient's detoxification capacity and other genetic factors may play a crucial role in the patient's recovery. During rehabilitation, the patient's physician should consider prescribing supporting therapy, such as antioxidant treatment.

Conclusion

Dental materials and implants can induce sensitization in genetically susceptible individuals. The frequency of metal allergy is significantly higher in patients with autoimmune disorders and CFS than in healthy controls. Metal allergy can be tested by patch test (*in vivo*) and by LTT (*in vitro*). The identification of metal-sensitive patients is the first step to successful treatment, which may involve RID. Many case reports and clinical studies show that the replacement of amalgam or other metal alloys in allergic individuals can lead to dramatic clinical improvement. To avoid side-effects, it is important to follow a strict working protocol, which minimizes the risk of metal exposure for the patient.

Acknowledgement

The authors wish to thank Margit Forsbeck MD and Jan Marcusson MD for the skillful performance of patch tests, and to Linda Nelson for the help with the preparation of the manuscript.

This work was supported by grant NR 9414-3 of the Internal Grant Agency of Ministry of Health, Czech Republic, which is gratefully acknowledged.

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