Environmental illness: evaluation of salivary flow, symptoms, diseases, medications, and psychological factors

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Patients with symptoms allegedly caused by abnormal sensitivity to dental fillings and/or to electromagnetic fields and other environmental factors frequently report oral complaints. Forty-four consecutive patients with these symptoms were studied. The aim was to investigate whether unstimulated salivary flow rate was associated with *Candida*, symptoms, disease, medication, age, sex, anxiety, depression, and stress. Furthermore, the aim was to compare the level of anxiety, depression, and stress in these patients with an age- and sex-matched control group. Fifty percent had no or low flow rate from the minor salivary glands. *Candida* pseudohyphae were found in 50% of the patients. Hypothyroidism and/or intake of thyroid hormones, headache, fatigue, and age were negatively associated with unstimulated salivary flow rate, and dizziness was positively associated. Unstimulated salivary flow rate was positively associated with stimulated salivary flow rate and flow rate from the minor salivary glands. Burning mouth and subjective oral dryness were reported by 48%, and 46%, respectively. The patients were more anxious, stressed, and especially more depressed than the control group. Unstimulated salivary flow rate was negatively associated with state anxiety. Measurement of salivary flow rate is important in patients with environmental illness and can be used in combination with other measurements as a diagnostic tool.
☐ *Anxiety; depression; enviromental illness; hypothyroidism; saliva*

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Patients with environmental illness represent a heterogeneous group of individuals with symptoms allegedly caused by abnormal sensitivity to chemicals, such as dental fillings, and to electromagnetic fields or other environmental factors (1, 2). Oral symptoms such as dry mouth and burning mouth are common complaints and often lead patients to consult their dentist (3, 4). Other frequently reported symptoms are fatigue and dizziness and symptoms involving the eyes and skin.

It has been proposed that the etiology of environmental illness could be a physical or psychophysiological reaction to multiple environmental factors, a misdiagnosed physical or psychological illness, or a manifestation of culturally shaped illness behavior (1).

Saliva plays an important role in maintaining oral health. A reduced flow rate may result in increased prevalence of oral disease and complaints (5–8). Although the minor salivary glands contribute up to 10% of the total volume of saliva (9), most research concerns the major salivary glands and whole saliva (10–12). Shern et al. (13) studied the flow rate of healthy unmedicated individuals and found no association between the flow rate for whole saliva and that for the minor salivary glands.

Many diseases and more than 400 medications have been reported to induce salivary gland hypofunction and/or cause subjective oral dryness (14, 15). Psychological processes may also reduce salivary flow or cause oral complaints (16, 17). Few studies have investigated whether there is an association between medications and psychological factors and salivary flow rate. In a study of anxiety, depression, stress, and medication we found that medications were the most important factor for hyposalivation, whereas the psychological factors were more associated with subjective oral dryness (18).

The variety of reported complaints allegedly caused by environmental factors requires an evaluation of medical, dental, and psychological factors in this patient group to develop adequate treatment modalities.

The aim of this study was to investigate whether unstimulated salivary flow rate was associated with the presence of *Candida*, oral and general symptoms, disease, intake of medication, age, sex, anxiety, depression, and stress in patients with symptoms allegedly caused by dental fillings and/or electromagnetic fields. Furthermore, the aim was to assess the level of anxiety, depression, and stress in this patient group.

Materials and methods

Subjects

Forty-four consecutive patients referred to the School of Dentistry, Umeå University, for symptoms allegedly caused by abnormal sensitivity to either dental fillings or electromagnetic fields, or to both, were included in the study. Twenty-five were women (57%) with a mean age of 48 years (range, 34–79 years) and 19 were men (43%) with a mean age of 45 years (range, 32–64 years). All participants gave their informed consent. The Ethics Committee for Human Experiments at Umeå University approved the study.

Registration of diseases, various symptoms, and intake of medication

All patients were interviewed by experienced dentists with regard to current diseases, symptom profile, and current medication. General diseases were classified in accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (19). Medication was classified in accordance with the WHO guidelines for Anatomical-Therapeutical-Chemical (ATC) (20).

Determination of flow rate from the minor salivary glands, and flow rate of whole saliva

Experienced dentists performed the clinical investigation. They had received hands-on training and were calibrated before the start of the study. The patients were instructed to refrain from smoking, eating, or drinking for at least 1 h before the test session.

After the mucosa had been dried with a cotton pad the unstimulated flow rate from the lower labial minor salivary glands was assessed by inspection of the lower labial mucosa near the midline for 5 min. The flow rate from the unstimulated lower labial minor salivary glands was classified into two groups: 0 = no to low flow with drops of saliva <1 mm in diameter, and 1 = average to high flow with drops of saliva >1 mm in diameter. The flow rates of whole saliva were determined by using the draining and masticatory methods (21). Unstimulated whole saliva was collected for 10 min. The patient first swallowed to clear the mouth of saliva, and then saliva was drooled into a centrifuge glass tube. Collection time was reduced or extended in some rare cases (range, 5–15 min). Subsequently, whole saliva was measured during stimulation provided by chewing standardized paraffin (1 g; melting point, 39°C) for 3 min. Before collection, the paraffin was chewed to softness, after which saliva was swallowed. In some cases collection time was reduced or extended (range, 1.5–5 min). All saliva produced was delivered into a centrifuge glass tube graded in 0.1-mL increments up to 10 mL (KEBO lab AB, Spånga, Sweden).

Assessment of oral complaints and presence of Candida

The presence of burning mouth and oral dryness was registered. Clinical protocols designed for this purpose were used together with interviews. Smears were taken from the buccal oral mucosa and tongue in accordance with a standardized procedure from the Department of Oral Pathology. For the detection of *Candida* pseudohyphae, slides were first stained with periodic acid-Schiff (PAS) and then screened by means of a conventional light microscope at ×10 magnification.

Assessment of anxiety, depression, and stress

Anxiety, depression, and stress were assessed in the 44 patients and in 44 age- and sex-matched healthy controls who had no disease or intake of medication. The controls were from a study population in whom salivary flow and oral complaints had been studied in 1202 individuals (655 women, 547 men) in relation to medication, anxiety, depression, and stress (18). The State-Trait Anxiety Inventory (STAI) was used to assess state and trait anxiety (22). State anxiety is considered to be transitory and describes experiences such as apprehension, tension, and worry. A higher level of anxiety trait increases the probability of experiencing an increase in state anxiety when exposed to threat. The STAI consists of 40 items, 20 items each for both the STAI state anxiety scale and the STAI trait anxiety scale. The items are scored on 4-point intensity scales.

The Swedish version of the revised 21-item Beck Depression Inventory (BDI) was administered to assess the level of depression (23). The BDI focuses on affective, cognitive, somatic, and behavioral aspects of depression. The items are rated from 0 to 3 in terms of intensity, and the total BDI score ranges from 0 to 63. BDI scores of 10–18 describe mild to moderate depression, scores of 19–29 moderate depression, and scores of 30–63 severe depression (23).

The General Perceived Stress Questionnaire (PSQ) measures general stress perceived during the past few years (24). The PSQ focuses on cognitive perceptions rather than emotional states or specific life events. The PSQ is a

Table 1. The distribution of diseases and intake of medication in the patient group, various general and oral symptoms in the patient group, and lower labial minor salivary glands flow rate and *Candida* in the patient group

	No.	%	Women	Men
Diseases and medication				
Asthma	5	11	3	2
Cardiovascular disease	4	9	2	2
Hypothyroidism	4	9	4	0
Intake of medications	21	48	13	8
Intake of analgesics	8	18	8	0
Intake of psychotropics	5	11	2	3
Antiasthmatics	5	11	3	2
Intake of thyroid hormones	4	9	4	0
Intake of antihypertensives	3	7	1	2
Symptoms				
Skin complaints	24	55	16	8
Fatigue	18	41	12	6
Various eye symptoms	16	36	11	5
Pain	15	34	10	5
Headache	14	32	9	5
Gastrointestinal symptoms	10	23	5	5
Lack of concentration	7	16	4	3
Various allergic reactions	6	14	4	2
Dizziness	6	14	3	3
Sleep disturbances	5	11	2	3
Burning mouth	21	48	13	8
Subjective oral dryness	20	46	12	8
Minor flow and *Candida*				
No and low minor salivary flow	22	50	15	7
Candida	22	50	15	7

Table 2. The range, mean values, and standard deviation (*s*) for age and whole salivary flow rate in the patient group

Variable	All				Women				Men			
	Min	Max	Mean	*s*	Min	Max	Mean	*s*	Min	Max	Mean	*s*
Age, years	32	79	46.7	9.71	34	79	48.0	10.69	32	64	45.0	8.20
Unstimulated salivary flow, mL/min	0.00	0.87	0.30	0.17	0.00	0.87	0.27	0.19	0.01	1.00	0.38	0.21
Stimulated salivary flow, mL/min	0.29	3.70	1.79	0.85	0.29	3.07	1.42	0.64	0.98	4.00	2.35	0.93

30-item questionnaire, and the items are scored from 1 to 4. A PSQ Index is computed from the total raw score.

Statistical methods

The correlation between the unstimulated salivary flow rate and the variables of interest was analyzed by using Spearman's rho correlation coefficient. Multiple linear regression with backward elimination was applied with unstimulated salivary flow rate as dependent variable, to test the psychological factors. Differences in BDI, STAI, and PSQ scores for the patients and the control group were tested by means of non-parametric comparison of the two groups by using the Mann–Whitney test. The 5% level was chosen as a guideline for statistical significance. Statistical routines from the SPSS for Windows were used.

The differences in various variables were detected by partial least-squares analysis (PLS). This method is powerful when few individuals and many variables are studied. PLS optimizes the relation between all variables (X variables) and the unstimulated salivary flow rate (Y variable). The PLS results in a projection of the X variables and the Y variable on several significant information-bearing dimensions (25–27). All the variables are plotted, and the loading plots yield information about which variables contribute most information to the plot. The PLS discriminate analysis (PLS-DA) was used to compare the ratings of the BDI, STAI, and PSQ in the patients and the controls. To evaluate the importance of terms in the model, the variable importance in the projection (VIP) value was used. The VIP gives the influence of every term in the matrix X on the Y variables. Variables with VIP >1.0 are the most relevant for explaining Y. The fraction of the total variation of the Xs can be predicted by Q^2 (goodness of prediction). When Q^2 for the whole data set is larger than the significance limit, the tested dimension is considered significant. SIMCA-S for Windows was used to perform the PLS, PLS-DA, and VIP (28).

Results

Diseases, various symptoms, and intake of medication

The patients reported diseases such as asthma, cardiovascular disease, and hypothyroidism. The most frequent complaints reported were skin complaints, fatigue, various eye symptoms, musculoskeletal pain, and headache. Analgesics, psychotropics, and antiasthmatics were the medicines most frequently taken (Table 1). Twenty-one patients (48%) took medication, nine patients had intake of more than one type of medication, and six patients took three or more medications.

Flow rate from the lower labial minor salivary glands and flow rate of whole saliva

No or low unstimulated salivary flow rate from the lower labial minor salivary glands was found in 50% of the

Table 3. Spearman's rho correlation coefficients, and the variables' importance in the projection (VIP) values between unstimulated salivary flow rate and studied variables in the patient group

Variable	Spearman's rho correlation coefficient	VIP
Minor salivary glands	0.485**	2.18
Hypothyroidism	−0.455**	1.91
Intake of thyroid hormones	−0.455**	1.91
Headache	−0.302*	1.58
Stimulated salivary flow	0.390**	1.43
Fatigue	−0.255	1.38
Dizziness	0.402**	1.32
Age	−0.169	1.24
Sex	−0.273	0.97
Candida	−0.220	0.94
Lack of concentration	−0.208	0.93
State anxiety (STAI)	0.050	0.92
Subjective oral dryness	−0.130	0.92
Medication	−0.154	0.83
Burning mouth	−0.192	0.77
Allergic reaction	0.037	0.66
Pain	0.013	0.66
Skin complaints	0.099	0.65
Various eye symptoms	−0.002	0.55
Gastrointestinal symptoms	−0.077	0.45
Intake of psychotropics	0.062	0.43
Intake of antihypertensives	0.110	0.38
Trait anxiety (STAI)	−0.047	0.30
Antiasthmatics	−0.042	0.25
Asthma	−0.042	0.25
Intake of analgesics	−0.132	0.24
Cardiovascular disease	−0.006	0.24
Sleep disturbances	0.104	0.23
Perceived stress (PSQ)	0.040	0.18
Depression (BDI)	0.110	0.01

** = $P < 0.01$;
* = $P < 0.05$.

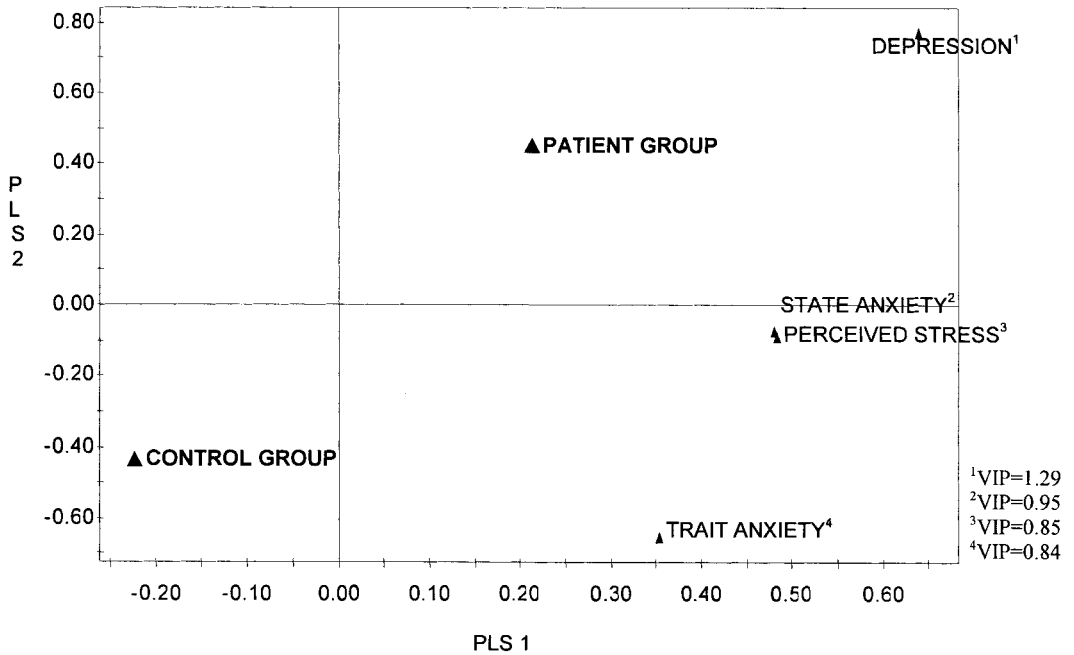

Fig. 1. Partial least-squares discriminate analysis (PLS-DA). Psychological factors in the patient group and age- and sex-matched controls. Variables with VIP values >1.0 are most important. The distance from the patient and the control group reflects the differences between the groups as explained by the variables.

patients (Table 1). The unstimulated salivary mean flow rate was 0.30 mL/min, and the stimulated salivary mean flow rate was 1.79 mL/min (Table 2). Five patients (11%) (4 women) had an unstimulated salivary flow rate <0.1 mL/min, and they reported hypothyroidism, fatigue, and headache. Three women (7%) had a stimulated salivary flow rate <0.7 mL/min, and they reported hypothyroidism and headache.

Oral complaints and presence of Candida

Burning mouth and subjective oral dryness were reported by 21 (48%) and 20 (46%) of the patients, respectively. Thirteen women (52%) had burning mouth, and 12 (48 %) reported having subjective oral dryness. Six women and four men (23%) had both symptoms. Fifteen percent of those with burning mouth and 20% with subjective oral dryness had an unstimulated salivary flow rate <0.1 mL/min. *Candida* pseudohyphae were found in 50% of the patients (Table 1).

Anxiety, depression, and stress

In comparing the patients and the controls we found that the patients had higher scores on the BDI (Mann–Whitney: $z = -4.125$, $P < 0.001$), the PSQ (Mann–Whitney: $z = -2.588$, $P < 0.01$), the STAI state scale (Mann–Whitney: $z = -2.436$, $P < 0.05$), and the STAI trait scale (Mann–Whitney: $z = -1.662$, NS). Ten patients (23%) had a BDI > 10. Multiple linear regression showed negative association between unstimulated salivary flow rate and the STAI state anxiety scale ($P < 0.05$). The further analysis with PLS-DA ($Q^2 = 0.134$; model significant) showed that the BDI had a VIP value >1.0 (Fig. 1).

Unstimulated salivary flow rate and associated variables

By using bivariate non-parametric correlation, a positive correlation was found in the patients between the unstimulated salivary flow rate, the unstimulated salivary flow rate from the lower labial minor salivary glands, and stimulated salivary flow rate. Dizziness also had a positive correlation with unstimulated salivary flow rate. Negative correlation was found between the unstimulated salivary flow rate and hypothyroidism, intake of thyroid hormones, and headache (Table 3). This association was further explored by using the PLS ($Q^2 = 0.216$; model significant). The results of this analysis showed that the unstimulated salivary flow rate was significantly associated (VIP > 1.0) with unstimulated salivary flow rate from the lower labial minor salivary glands, hypothyroidism, intake of thyroid hormones, headache, stimulated salivary flow rate, fatigue, dizziness, and age (Fig. 2, Table 3). Female sex, presence of *Candida* pseudohyphae, lack of concentration, state anxiety (STAI), and subjective oral dryness had VIP values just below 1.0.

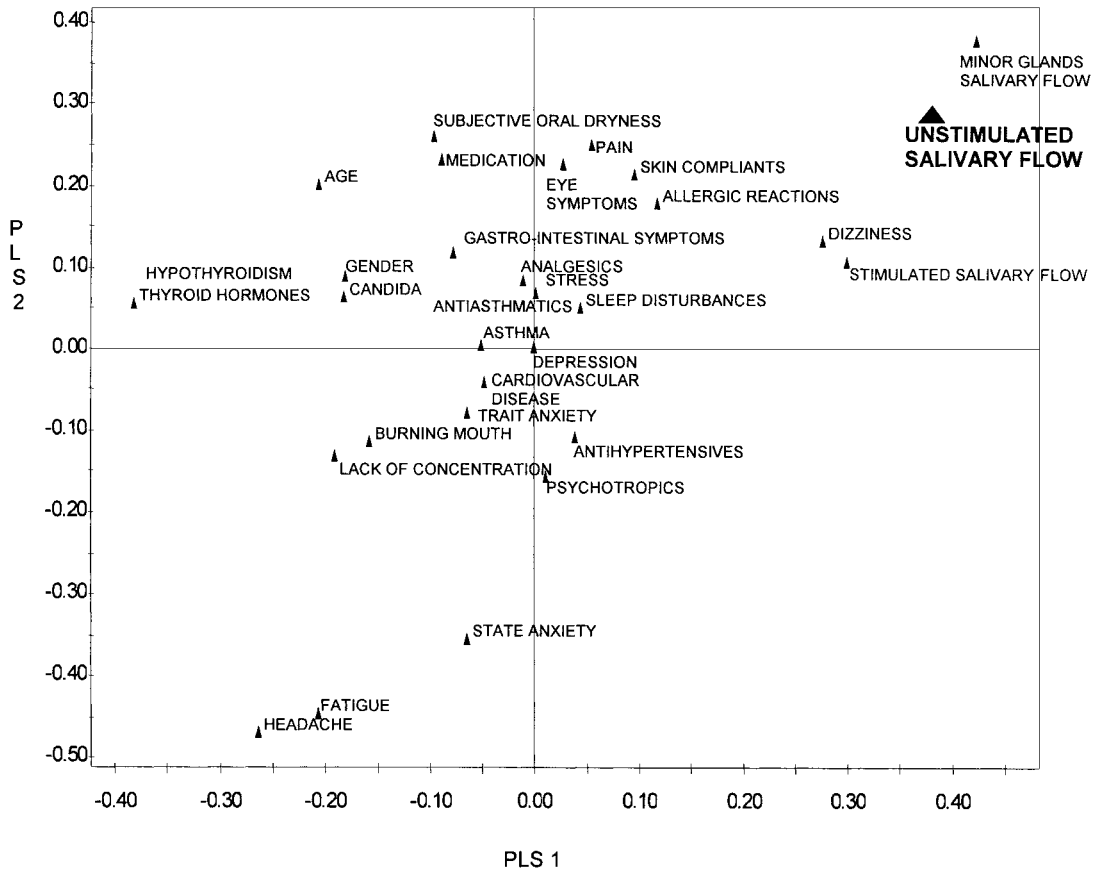

Fig. 2. Partial least-squares analysis (PLS). Unstimulated salivary flow rate (Y variable) and all studied variables (X variables). Projections for the variables are plotted in a two-dimensional window created by the two descriptors PLS1 and PLS2. The distance from the y-variable (unstimulated salivary flow rate) show the association of the studied variables.

Discussion

The patients in the present study were referred to the School of Dentistry because they had symptoms that they thought were caused by environmental factors, but the symptoms in such patients are often a result of a complex pattern of interacting factors of both somatic and mental origin (1).

Oral complaints are common among these patients (3, 4). This was confirmed in this study, in which 48% had burning mouth, and 46% had subjective oral dryness, which is a much higher frequency than in a normal population (8). In contrast to an earlier study (8) we found only a tendency towards a connection between reduced salivary flow rate and subjective oral dryness. The mean unstimulated salivary flow rate in the patients studied was normal, which is the same as reported in other studies (8, 29), and our findings support the thesis that elderly women have a reduced unstimulated salivary flow rate (8, 10). Headache and fatigue were also associated with a reduced unstimulated salivary flow rate, in contrast to dizziness, which increased the unstimulated flow rate. This may be the result of a combination of many interacting factors not easily explained, but dizziness is common in combination with feeling sick, which is known to increase the salivary flow rate.

A significant association was found between the unstimulated salivary flow rate, the stimulated salivary flow rate, and the unstimulated salivary flow rate from the lower labial minor salivary glands, which contrasts with a study by Shern et al. in healthy individuals (13). Fifty percent of the patients had no or low flow rate from the lower labial minor salivary glands. The cause of a reduced secretion of these glands is still unknown, but it has been suggested that the side effects of medication and psychological processes play an important role (7). The procedure used in this study to quantify the flow rate from the lower labial minor salivary glands may have some disadvantages, but our aim is to point out the importance of assessing the flow rate from the minor salivary glands in patients.

Diseases such as Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus and intake of psychotropics, antihypertensives, and antihistamines are most commonly associated with reduced salivary flow rate (14, 15). Hypothyroidism is often a disease with complex

clinical features, and the diagnosis of a thyroid disease is mainly made on clinical grounds, from examination, history, and laboratory tests. In the present study hypothyroidism and/or intake of thyroid hormones was found to be associated with reduced unstimulated salivary flow rate. None of the patients had been exposed to internal radionuclides for thyroid malignancy, which could have explained the reduction in salivary flow rate. In a study of 259 elderly volunteers (70 ± 4.5 years) hypothyroidism was found in the group with an unstimulated salivary flow rate < 0.1 mL/min but not in the group with a higher unstimulated salivary flow rate (30). Persson et al. (31) also found that hypothyroidism significantly reduced stimulated salivary flow rate. We have found that intake of thyroid hormones, stimulated salivary flow rate, depression, and trait anxiety were significantly associated with burning mouth syndrome (27). This illustrates the problems involved in the diagnosis of patients with putative environmental illness. The question in this case is whether the hypothyroidism itself or the intake of thyroid hormones caused the reduction of salivary flow rate.

Patients with symptoms allegedly caused by electromagnetic fields have been described as distressed (32), and when the results of the psychological investigation were compared with the scores for the control group, the patients in the present study proved to be more depressed, anxious, and stressed on the basis of the BDI, STAI, and PSQ. The levels of depression and anxiety are lower than one might expect in psychiatric patients, but 23% in this study were mildly to severely depressed. When comparing the patients and the controls by means of a multivariate method (PLS-DA), we found that depression was the significant psychological factor in the patients. This finding has an important clinical impact because the clinician has to be more empathic and caretaking and pay more attention when investigating and treating a depressed patient. Another finding was that the anxiety state was more important than the anxiety trait in the patients, which indicates that these patients do not have an anxiety-prone personality. The presence of depression, anxiety, stress, and physical symptoms supports the view that the patients with symptoms allegedly caused by dental fillings and/or electromagnetic fields should be labeled as having a somatization syndrome; that is, they experience and communicate mental distress as physical symptoms and therefore seek professional medical/odontological help (2, 33, 34).

Unstimulated salivary flow rate and state anxiety were associated, which may indicate that the patients with environmental illness and a low unstimulated salivary flow rate have a higher level of state anxiety. This association between the unstimulated salivary flow rate and state anxiety also makes it possible to use the unstimulated salivary flow rate as a marker of state anxiety.

Clearly, patients with environmental illness have pronounced oral complaints, which impact negatively on their lives. Collaboration with professionals from various disciplines is important in handling and evaluating these patients to provide them with adequate treatment and prevent further disabling complaints and disease. As salivary flow rate varies among individuals and also in the same individual under different conditions, standardized collection methods over time are needed (35). When handling patients with complex states, such as environmental illness, it is important to bear in mind the finding that reduction in the unstimulated salivary flow rate is common in patients with hypothyroidism and/or intake of thyroid hormones. Therefore, assessment of salivary flow rate can be used in combination with other measurements as a diagnostic tool for obtaining a better understanding of these patients.

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