KEY WORDS
Temporomandibular disorder, Thyroid diseases, Levothyroxine

Cross-sectional study

ASSOCIATION BETWEEN THYROID HORMONE INTAKE AND TEMPOROMANDIBULAR DISORDER: A CROSS-SECTIONAL STUDY

VALENTINA GIULIANI, PhD DDS
Department of Experimental and Clinical Medicine, University of Florence, Italy

MICHELE NIERI, PhD DDS
Department of Experimental and Clinical Medicine, University of Florence, Italy

DEBORA FRANCESCHI, DDS
Department of Experimental and Clinical Medicine, University of Florence, Italy

IRENE BOTTACCI, DDS
Department of Experimental and Clinical Medicine, University of Florence, Italy

FELICITA PIERLEONI, MDM
Department of Experimental and Clinical Medicine, University of Florence, Italy

Correspondence to
Valentina Giuliani
dr.v.giuliani@gmail.com

PURPOSE. Temporomandibular disorder (TMD) consists of multifactorial pathologies of the temporomandibular joint and its surrounding structures. Thyroid hormones affect metabolism, growth, contractile function, and regeneration of muscles. The aim of this cross-sectional study was to investigate the association between intake of a thyroid hormone drug (levothyroxine) and TMD in an adult population.

MATERIALS AND METHODS. Adult patients referred to University of Florence for a dental visit were included in the present study. During the first appointment, personal, medical history and clinical data were recorded, and thyroid hormone drug (levothyroxine) regimen noted. Fonseca Anamnestic Index was used to classify patients as with or without TMD, and the resulting data was then subjected to logistic regression analysis.

RESULTS. Of a total of 1212 patients included, 124 (10.2%) were taking levothyroxine and 271 (22.4%) suffering from at least mild TMD. Seventy-eight (6.4% of the total sample) were classified as having severe TMD, while the remaining 941 (77.6%) had no history of TMD. The data collected indicates that TMD is more frequent in young, female, non-smoking patients using levothyroxine (OR = 2.64 95% CI from 1.74 to 4.00; P <0.0001). Severe TMD was more frequent in young female patients, in whom, however, the association with levothyroxine intake was not significant (OR=0.53 95% CI from 0.15 to 1.56 P=0.2531).

CONCLUSIONS. Levothyroxine intake, as well as the age and sex of the patient, is correlated with the presence of TMD.

CONFLICT OF INTEREST STATEMENT
This study was completely self-funded, and no financial support was sought or obtained, not even in the form of free materials.

INTRODUCTION

Temporomandibular disorder (TMD) is an umbrella term for a variety of pain and dysfunction linked to the temporomandibular region, masticatory muscles and temporomandibular joint[1-4]. Several psychosocial and behavioural factors (anxiety, depression, and stress), are significantly associated with TMD symptoms[5-8]. The multifactorial aetiology of TMD[9,10] means that it requires a multidisciplinary approach that includes the evaluation of psychological components[11].

The thyroid, like other human endocrine glands, exerts wide-ranging effects on multiple organs, in particular the heart, musculoskeletal apparatus and nervous system[12,13]. Thyroid hormones affect metabolism, growth, contractile function, and regeneration of muscles[12,14,15]. In addition, thyroid dysfunction has been associated with neuropsychiatric disturbances, including mood disorders like anxiety and depression. Both over- and underactivity of the thyroid

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gland can lead to muscle dysfunction, like myopathies and trigger point, as well as affecting the relationship between mood and cognitive dysfunction[15-18]. In hypothyroidism, whether due to congenital or acquired pathologies, levothyroxine sodium products are the standard treatment[19]; this class of drug is one of the most commonly administered in both Italy and the US[20-22].

Since thyroid hormone targets the musculoskeletal and nervous systems, the correlation between TMD and thyroid diseases warrants investigation. However, only a few studies have evaluated the association between thyroid and TM dysfunction[23-26]. Hence, the aim of this cross-sectional study was to investigate the association between intake of thyroid hormone drugs (levothyroxine) and TMD in an adult population. To our knowledge, this is the first study to investigate the prevalence of TMD in patients taking thyroid hormones (levothyroxine).

MATERIALS AND METHODS

Study design, examination methods and protocol

The study design, a cross-sectional comparison of the prevalence of levothyroxine intake in a population with and without TMD, is reported in accordance with the STROBE statement[27].

Patient data, retrieved from the First Visit Electronic Record database (FVER), was recorded following the first dental examination conducted at the University of Florence Department of Experimental and Clinical Medicine, from 1 January 2016 to 1 March 2020, when Covid pandemic lockdown measures prevented further recruitment.

Inclusion criteria for the sample were:

- age between 18 and 90 years;
- complete anamnestic records.

Exclusion criteria were:

- any medical or dental urgencies (i.e., acute pain with muscle spasm/contraction, polyarthritis, acute maxillofacial trauma, acute dental pulpitis, pericoronitis of third molar) indicated by medical or dental anamnestic history and clinical and instrumental dental examination;
- patients with neurological, vascular or psychiatric disorders (e.g., trigeminal neuralgia, migraine headaches, neoplasia, etc).;
- edentulous patients (who would be unable to respond to items on the Fonseca Anamnestic Index.

The FVER database used for patient selection was developed using FileMaker Pro for Macintosh/Windows versions 15 (FileMaker, Santa Clara, CA, US), and is accessed by the Department's Dental Medical Doctors (DMDs) at the end of the first dental visit to record each patient's personal information, medical history, clinical data and X-rays. Three expert DMDs conducted the first visit, following a standardized procedural protocol approved by the University of Florence Department of Clinical and Experimental Medicine, Dentistry section. TMD was assessed using the Fonseca Anamnestic Index (FAI)[28,29]. The FAI index comprises 10 items with 3 response options, scored as follows: "yes" (10 points), "sometimes" (5 points) and "no" (0 points). The patients were instructed to reply to the ten questions, choosing one of the answers to indicate the different degrees of TMD (**TABLE 1**). The final score was determined by summing the points scored for all items, allowing the following classification: no signs and symptoms of TMD (0-15 points), mild TMD (20-40 points), moderate TMD (45-60 points), and severe TMD (70-100 points). Affermative answers on the questionnaire were considered to indicate at least mild TMD. A separate analysis was performed on data from patients with severe TMD.

TABLE 1 FONSECA QUESTIONNAIRE

Numbers	Questions
1	Do you have difficulty opening your mouth wide?
2	Do you have difficulty moving your jaw to the side?
3	Do you feel fatigue or muscle pain when you chew?
4	Do you have frequent headaches
5	Do you have neck pain or a stiff neck?
6	Do you have ear aches or pain in that area (TMJ)?
7	Have you ever noticed any noise in your TMJ while chewing or opening your mouth?
8	Do you have any habits such as clenching or grinding teeth?
9	Do you feel that your teeth do not come together well?
10	Do you consider yourself a tense (nervous) person?

TABLE 2 FONSECA INDEX. THE NUMERIC DISTRIBUTION OF THE CLINICAL DYSFUNCTION INDEX: 0 NO CLINICAL SYMPTOMS, 1 MILD CLINICAL SYMPTOMS, 2 MODERATE CLINICAL SYMPTOMS, 3 SEVERE CLINICAL SYMPTOMS.

Class TMJ	Frequency	Percentage
0	941	77.6
1	95	7.8
2	98	8.1
3	78	6.4
Total	1212	100

During the first dental visit, drug history was ascertained, including a specific question about the consumption of thyroid hormone therapy (levothyroxine) to correct the dysfunction of endocrine glands, and this information too was recorded in the FVER database.

Statistical analysis

Data on quantitative variables is expressed as mean and standard deviation, while data on qualitative variables is expressed as percentage and frequency. Logistic regression for TMD (at least mild) was performed using age, gender, smoking status, and levothyroxine as explicative variables. The same analysis was performed considering severe TMD as the outcome variable.

RESULTS

Out of 1212 patients examined, 722 were women (59.6%) and 490 were men (40.4%). The mean age of the patients was 49.8±17.3 years (minimum = 18 years, maximum = 80 years); 184 patients were smokers and 124 (10.2%) patients were taking levothyroxine. Overall 271 patients (22.4%) suffered from at least mild TMD, of which 78 (6.4% of the total) were classified as having severe TMD. The remaining 941 (77.6%) had no history of TMD (**TABLE 2**). Descriptive statistics of patients with and without TMD are reported in **TABLE 3** and **TABLE 4**, respectively.

TABLE 3 DESCRIPTIVE STATISTICS OF PATIENTS WITH AND WITHOUT TEMPOROMANDIBULAR DISORDER

Variable	TMD (at least mild) n = 271	No TMD n = 941	Total n = 1212
Age (years)	43.1 ± 15.5	51.8 ± 17.3	49.8 ± 17.3
Gender (female)	207	515	722
Gender (male)	64	426	490
Smoker	24	160	184
No smoker	247	781	1028
Levothyroxine	50	74	124
No levothyroxine	221	867	1088

TABLE 4 DESCRIPTIVE STATISTICS OF PATIENTS WITH AND WITHOUT SEVERE TEMPOROMANDIBULAR DISORDER

Variable	Severe TMD n = 78	NO Severe TMD n = 1134	Total n = 1212
Age years	31.9 ± 9.3	51.1 ± 17.0	49.8 ± 17.3
Gender (female)	62	660	722
Gender (male)	16	474	490
Smoker	9	175	184
No smoker	69	959	1028
Levothyroxine	4	120	124
No levothyroxine	74	1014	1088

According to our analysis, TMD was more frequent in young, female, non-smokers and in those being treated with levothyroxine (OR = 2.64; 95% CI from 1.74 to 4.00; P <0.0001) (**TABLE 5**). Severe TMD was more prevalent in the young, female population (**TABLE 6**), in whom the consumption of levothyroxine had no significant link with TMD (OR = 0.53; 95% CI from 0.18 to 1.56; P = 0.2531) (**TABLE 6**).

DISCUSSION

This is the first study to explore the relationship between the consumption of thyroid hormone and the prevalence of TMD in a population referred to a dental clinic for general dental examination during the four years before the Covid pandemic. In this cross-sectional study, four major variables were investigated, namely sex, age, smoking habits and levothyroxine intake, in a population divided by the presence or absence of TMD. Our findings revealed that there does appear to be a correlation between levothyroxine intake and TMD, but only when the severity of disease was not considered. No significant association with levothyroxine consumption was found in patients with severe TMD.

In a previous study, the potential relationship between TMD and chronic disorders, including thyroid dysfunction, in terms of hypo- and hyperthyroidism, were recently investigated in a

TABLE 5 LOGISTIC REGRESSION FOR PRESENCE OF TMD

Variable	Odds ratio	95%CI	P-value
Age	0.97	0.96; 0.98	< 0.0001
Gender (F)	2.33	1.69; 3.21	< 0.0001
Smoking	0.53	0.33; 0.85	0.0087
Levothyroxine	2.64	1.74; 4.00	< 0.0001

TABLE 6 LOGISTIC REGRESSION ANALYSIS ON THE SEVERE TMD GROUP

Variable	Odds ratio	95%CI	P-value
Age	0.92	0.90; 0.94	<0.0001
Gender (F)	3.08	1.71; 5.55	0.0002
Smoking	0.89	0.42; 1.89	0.7608
Levothyroxine	0.53	0.18; 1.56	0.2531

large-scale nationwide South Korean study. The odds ratio for TMD prevalence was 1.49 in cases of thyroid dysfunction, and as with our patient set, TMD prevalence was higher in young females and smokers[26]. In a retrospective study, Byra et al. corroborated the correlation between signs and symptoms of TMDs and thyroid pathology both in case of hypothyroidism and hyperthyroidism[25]. However, it is important to note that the present study was not designed to investigate the association between thyroid disease and TMD, but rather the potential role of levothyroxine as "wake-up call" for temporomandibular diseases, which are not easy for general dentistry practitioners to diagnose during the first patient visit.

To date, when the range of thyroid disease has been reduced to hypo-functionality, the evidence demonstrating the correlation between consumption of thyroid hormone and TMD is weak. Nonetheless, Grozdinska et al. found a high statistical prevalence of TMD in a female population with Hashimoto thyroiditis (HT group) with respect to a female population without HT (control group); in these cases, only those who developed hypothyroidism received replacement hormones as therapy[24]. In the presence of TMD, the clinical dysfunction, judged using the Fonseca index, was significantly higher in the HT group than the control group, and in the latter, no severe cases of TMD were documented. The authors reported that autoimmune thyroid gland dysfunction could interfere with masticatory activities, as thyroid hormones influence muscle development, regeneration and contractile function. Furthermore, chronic muscle imbalance could lead to chronic pain and stress[30,31]. The literature also supports our finding that TMD is more prevalent in young females[32]. In fact, even though Grozdinska's study[24] was limited to a female population, the role of gonadal steroid hormone in the high incidence of TMD pain in women was emphasized[33]. Moreover, sex hormones can be considered a risk factor for both hypo- and hyperthyroid dysfunction[34]. The above findings are partially in line with those from the present study, which supported a higher TMD frequency in young, female non-smokers taking levothyroxine.

However, although the literature is generally in agreement regarding the higher prevalence of TMD in women[32,35], the age of the population studied has not always been reported. When

patient age was documented, however, TMD was more frequent in an older population, aged between 30 and 50 years[26,35].

Several epidemiological studies on the prevalence/incidence of TMD have examined socioeconomic and lifestyle characteristics in order to reveal whether or not they are significant factors in the TMD population with respect to a healthy population. Among these, smoking is one of the habits most frequently investigated. Although smoking is known to have adverse effects on bone metabolism; muscle strength, function and morphology; and pain[36-39], its effects on the presence, development and resolution of TMD warrants further discussion[40,41]. Smoking is a complex health behaviour driven by factors extending beyond nicotine dependence. A recent review has shown that the use of nicotine administered in different forms and ways improved positive social function, increasing self-reported states linked to social functioning[42], as well as having an acute analgesic effect[43]. All these factors may lead to TMD being underestimated in the smoking population, and may explain the apparently positive effect of smoking on TMD risk in the population with at least mild TMD (odds ratio 0.53). In the severe TMD group, however, smoking was not found to be a significant variable. Another potential explanation for this finding is the small number of smokers included in the sample; although the initial number of patients with severe TMD was 78, only 9 patients in that subpopulation were smokers, which may have reduced the significance of the results.

The main limitation of the present study was its cross-sectional design, and its analysis of data from a population, or a representative subset, *at a specific point in time.* Cross-sectional surveys do not normally indicate which variable is the cause and which is the effect. Hence, longitudinal cohort studies are required to verify the correlations found between levothyroxine and TMD. Another limitation was the discrepancy in diagnostic criteria between the Fonseca Anamnestic Index (FAI), used in the present study, and the more widely used Diagnostic Criteria for Temporomandibular Disorder (DC/TMD). Before the DC/TMD was introduced, the confused terminology prevented definition of a standardized tool for TMD assessment, leading to a difficult comparison of study results. DC/TMD now represents the gold standard, but it is reliant on evaluator training and experience[44,45]. The Fonseca Anamnestic Index (FAI), on the other hand, is a simple method of assessing the signs and symptoms of TMD and classifying the degree of severity. Being a patient-reported outcome method, it is suitable for examiners who are not TMD specialists, like the general dentists who conducted the first examinations in the present study.

CONCLUSIONS

TMD appears to be more frequent in patients taking levothyroxine, and also seems to be correlated with young age, female gender and non-smoking.

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