Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(2) 765–771

DOI: 10.1177/0300060518811009
journals.sagepub.com/home/imr
SAGE

Biochemical changes associated with temporomandibular disorders

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Abstract

Objective: To assess vitamin D, parathyroid hormone, calcitonin, calcium, phosphorus and magnesium levels in patients with versus without temporomandibular disorders (TMDs).

Methods: This prospective observational study included patients with TMDs and age-matched healthy controls. TMDs were diagnosed via physical and radiologic examination, and serum levels of 25 (OH) vitamin D, parathyroid hormone, calcitonin, calcium, magnesium, and phosphorus were determined. The impact of age, sex and seasonal variations in serum 25 (OH) vitamin D levels was controlled by the inclusion of age, sex and date-matched control patients.

Results: The study included 100 patients, comprising 50 patients with TMDs and 50 control patients. No statistically significant between-group differences were found regarding age or sex. No statistically significant between-group differences were found in terms of serum 25 (OH) vitamin D, calcitonin, calcium, magnesium or phosphorus levels. Parathyroid hormone levels were statistically significantly higher in patients with TMDs versus healthy control patients.

Conclusion: In patients with temporomandibular disorders, increased parathyroid hormone levels in response to vitamin D deficiency was significantly more prominent. These data suggest that, in patients with temporomandibular disorders, vitamin D deficiency should be assessed and corrected.

Keywords

Temporomandibular joint disorders, subluxation, disc displacement, vitamin D, parathyroid hormone, calcitonin, calcium homeostasis

Date received: 11 May 2018; accepted: 11 October 2018

Introduction

Temporomandibular disorders (TMDs) are a subgroup of joint and muscle disorders comprising muscle fatigue in the temporomandibular region, headache, disturbances

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in jaw movement, and articular sounds during mouth movements.[1] Affecting approximately 6–15% of the population, TMDs are relatively common and have a higher prevalence in women than men.[2] Although TMDs are considered to be a sub-classification of musculoskeletal disorders, the aetiological factors are not clearly understood but are thought to involve emotional tension, loss of teeth, postural deviation, masticator muscle dysfunction and alterations in temporomandibular joint structure.[3] The presence of varying degrees of inflammation has also been reported in certain TMDs.[4]

Vitamin D is an important component in calcium homeostasis, which is known to have a key role in bone health, including articular structures and muscles.[5] Not surprisingly, studies have shown an association between low vitamin D status and musculoskeletal disorders.[6–8]

The objective of the present study was to assess serum levels of vitamin D, parathyroid hormone, calcitonin, calcium, phosphorus and magnesium in patients with TMDs versus patients without TMDs. To the best of the authors' knowledge, the present report is the first published investigation of vitamin D levels and associated parameters in patients with TMDs.

Patients and methods

Study population and design

This prospective study included consecutive patients with TMDs and age/sex-matched healthy patients without TMDs (controls) who attended the Department of Plastic, Reconstructive and Aesthetic Surgery, Yuzuncu Yil University Hospital, Turkey, between December 2016 and September 2017. Ethics approval was obtained from the Yuzuncu Yil University Hospital ethics committee (decision number: 07; 28.12.2016), and all procedures were performed following Yuzuncu Yil University Hospital ethics committee standards, and in line with the 2000 edition of the Declaration of Helsinki, and with its later amendments or comparable ethical standards. Written informed consent was received from all participants included in the study.

Exclusion criteria included presence of temporomandibular joint ankyloses, dental or periodontal pathologies, drug misuse, smoking or alcohol misuse, presence of chronic renal failure (glomerular filtration rate <90 ml/min/1.73 m^2) or history of previous treatment for vitamin D deficiency.

Diagnosis of TMD

In patients with TMDs, the degree of mouth opening (with painless mouth opening as the main measure) was assessed with a caliper and evaluated using the patient's primary open bite or deep bite by the same experienced examiner (CYD). Diagnosis of closed lock was not established in any patient. Patients were diagnosed with TMD when three of the following six symptoms were identified: articular sounds, deviation of the jaw during opening, restricted mouth opening, articular pain, cervical or facial muscle pain, and tenderness of the masticator muscle on palpation.[9]

Direct spot temporomandibular joint radiographs (supplied by the Yuzuncu Yil University Department of Radiology) with both open and closed mouth were obtained to evaluate any abnormalities associated with this joint. If the direct radiographs were insufficient to obtain a diagnosis of TMD, the diagnosis was confirmed using magnetic resonance imaging (Yuzuncu Yil University Department of Radiology).

Sample collection and serum parameters

Venous blood samples (6 ml) were collected from all particpants following an overnight

fast, and were processed immediately upon collection. Blood samples were inclubated at –25°C for 30 min to allow clotting, then centrifuged at 4042 *g* for 5 min at –4°C for serum extraction. Serum samples were stored at –80°C before automated assessment for levels of the following factors using specified equipment according to the manufacturer's instructions: 25 (OH) vitamin D3, calcium, magnesium and phosphorus (assayed using an ARCHITECT *ci*16200 Integrated System and associated reagents; Abbott Core laboratory, Abbott Park, IL, USA), parathyroid hormone (ARCHITECT *i*4000*SR*; Abbott Core laboratory) and calcitonin (IMMULITE 2000 XPi immunoassay system; Siemens Healthcare GmbH, Erlangen, Germany). In order to eliminate the impact of age, sex and seasonal variations in serum 25 (OH) vitamin D levels, one age and sex-matched control patient was enrolled into the study at the same time as each patient with TMD.

Any patients found to have elevated parathyroid hormone levels were further evaluated regarding the underlying cause, and diagnosed with primary, secondary or tertiary hyperparathyroidism.

Statistical analyses

Categorical data are presented as *n* patient prevalence and continuous data are presented as mean ± SD. All data were analysed using IBM SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive (categorical) variables were compared using χ^2-test. Continuous data were assessed for normality of distribution using Kolmogorov–Smirnov test. Between-group differences in normally distributed variables were evaluated with the parametric Independent Samples *t*-test, and not-normally distributed variables were assessed using the non-parametric Mann–Whitney *U*-test. The confidence interval was taken as 95%, and *P* values <0.05 were considered to be statistically significant.

Results

A total of 100 patients were included in the study: 50 patients with TMDs (39 female and 11 male patients; mean age, 28.24 ± 10.41 years) and 50 control patients without any signs of symptoms of TMDs (38 female and 12 male patients; mean age, 30.90 ± 8.49 years). All patients with TMDs had temporomandibular joint disc displacement or temporomandibular joint subluxation with or without reduction. Between-group comparison of demographic and laboratory data are summarized in Table 1.

Between-group comparisons of biochemical results showed that there were no statistically significant differences in terms of serum 25 (OH) vitamin D3, calcitonin, calcium, magnesium or phosphorus levels. However, parathyroid hormone levels were found to be significantly higher in the TMDs group (78.05 ± 28.59 pg/ml) versus the control group (52.58 ± 18.20 pg/ml; $P < 0.001$; Table 1).

The distribution of patients having normal or elevated parathyroid hormone levels and normal or decreased 25 (OH) vitamin D3 levels were compared between the two groups (Table 2). Although the proportion of patients with vitamin D deficiency was similar in both groups; the proportion of patients with elevated parathyroid hormone levels was significantly higher in patients with TMDs (32/50 [64%]) compared with control patients (15/50 [30%]; $P < 0.001$; Table 2).

Patients with elevated parathyroid hormone levels ($n = 47$) were further evaluated regarding the underlying cause of hyperparathyroidism (primary, secondary or tertiary). In two of the patients, who were both in the TMDs group, parathyroid adenoma was determined as the cause of hyperparathyroidism (primary hyperparathyroidism).

Table 1. Demographic and laboratory characteristics in patients diagnosed with temporomandibular disorders (TMDs) and control patients without TMDs.

Characteristic	TMDs group ($n = 50$)	Control group ($n = 50$)	Statistical significance
Age, years	28.24 ± 10.41	30.90 ± 8.49	NS
Sex, female/male	39/11	38/12	NS
25 (OH) Vit D3, ng/ml (normal range, 20–100 ng/ml)	12.80 ± 6.08	14.86 ± 12.76	NS
PTH, pg/ml (normal range, 10–65 pg/ml)	78.05 ± 28.59	52.58 ± 18.20	$P < 0.001$
Calcitonin, pg/ml (normal range, <8.8 pg/ml)	3.14 ± 1.60	2.88 ± 1.19	NS
Calcium, mg/dl (normal range, 8.9–10.1 mg/dl)	9.69 ± 0.51	9.81 ± 0.40	NS
Magnesium, mg/dl (normal range, 1.7–2.4 mg/dl)	2.02 ± 0.17	2.01 ± 0.15	NS
Phosphorus, mg/dl (normal range, 2.5–4.5 mg/dl)	4.07 ± 4.79	3.32 ± 0.76	NS

Data presented as mean ± SD or *n* patient prevalence.
PTH, parathyroid hormone; 25 (OH) Vit D3, 25 hydroxy vitamin D3.
NS, no statistically significant between-group differences ($P > 0.05$; χ^2-test, independent samples *t*-test or Mann–Whitney *U*-test).

Table 2. Distribution of study participants (patients diagnosed with temporomandibular disorders [TMDs] and control patients without TMDs) regarding normal limits of serum parathyroid hormone and vitamin D.

Biochemical parameter	TMDs group ($n = 50$)	Control group ($n = 50$)	Statistical significance
PTH (normal/high)	18/32	35/15	$P = 0.001$
25 (OH) Vit D3 (normal/low)	7/43	10/40	NS

Data presented an *n* patient prevalence.
PTH, parathyroid hormone (normal range, 10–65 pg/ml); 25 (OH) Vit D3, 25 hydroxy vitamin D3 (normal range, 20–100 ng/ml).
NS, no statistically significant between-group differences ($P > 0.05$; χ^2-test).

In the remaining 45 patients, elevated parathyroid hormone levels were diagnosed as secondary hyperparathyroidism due to vitamin D deficiency. Tertiary hyperparathyroidism was not diagnosed in any of the cases.

Discussion

The aim of the present study was to investigate vitamin D status and relevant biochemical parameters in patients with TMDs, and compare results to those in patients without TMDs. The results revealed that in patients with TMDs, although there was not any statistically significant difference in vitamin D levels, parathyroid hormone levels were significantly higher compared with the control group. When the cause of this increase in parathyroid hormone levels was investigated, it was determined to be secondary

hyperparathyroidism in all except two patients with TMDs (two patients were diagnosed with parathyroid adenoma). Thus, it was shown that in patients with TMDs, elevations in parathyroid hormone levels in response to vitamin D deficiency were significantly more prominent. To the best of the authors' knowledge, this is the first study in the literature assessing the relationships of vitamin D status, parathyroid hormone levels and calcium metabolism in patients with TMD. Further studies into the effects of increased parathyroid hormone levels on the temporomandibular joint are warranted.

Temporomandibular disorders are a heterogeneous group of diseases involving the temporomandibular joint and related structures, mainly characterised by symptoms such as alterations in joint movement, articular sounds or pain.[1] TMDs are clinically important since they may disturb life quality in patients due to pain or alterations in joint movements causing difficulty in eating or speaking, and they are also important because their treatment is complex.[10] Although the aetiological factors that trigger TMDs remain unclear, biomechanical stress, oestrogen hormones and emotional stress have been defined as having a possible aetiological role.[11–13]

Vitamin D is a key element in calcium metabolism, and previous studies have shown that reduced serum levels of 25 (OH) vitamin D are associated with musculoskeletal disorders, such as chronic low back-leg pain and fibromyalgia, however, data regarding vitamin D status and TMDs are limited.[14,15] In an experimental model, Shen et al.[16] reported that vitamin D deficiency was correlated with an erosive temporomandibular joint osteoarthritis through induction of DNA damage and production of inflammatory cytokines. Decreased vitamin D levels have also been associated with radiographic changes in the temporomandibular joint.[17] However, the relationships between TMDs and vitamin D status, parathyroid hormone levels and calcium metabolism have not yet been evaluated in detail. In the present study, patients with TMDs were revealed to have significantly higher parathyroid hormone levels compared with control patients, while serum levels of vitamin D were low in both groups, and phosphorus and calcium were within normal ranges. No significant differences were found between the groups regarding serum calcitonin, calcium, magnesium, and phosphorus levels. The similar vitamin D deficiency rates in both groups may be related to the lack of a significant difference between the groups regarding calcium, magnesium and phosphorus levels.

In previous studies, the association between low vitamin D levels and augmented inflammation has been clearly defined,[18,19] however, the role of parathyroid hormone in this amplification remains unclear. Resolving vitamin D deficiency has been associated with better secondary hyperparathyroidism control and an improvement in inflammatory status in patients receiving haemodialysis.[20] Serum parathyroid hormone levels have been reported to be independently correlated with inflammatory markers including C-reactive protein, platelet-to-lymphocyte ratios, red cell distribution width, and presence of chronic inflammation.[21,22] Interestingly, in a recent study involving postmenopausal women, a positive correlation was reported between serum parathyroid hormone levels and the pro-inflammatory cytokines tumour necrosis factor-α, interleukin (IL)-1β, and IL-6.[23] In the present study, elevated parathyroid hormone levels and associated inflammation may be the main factors in the aetiopathogenesis of TMDs, however, the factors that trigger this increased parathyroid hormone response remain unknown.

Unfortunately, determination of serum vitamin D levels involves some methodological and clinical issues since serum levels of this vitamin may show some

seasonal variations, or variations due to sex, age, or body mass index.[24] Thus, it is not easy to determine the incidence of vitamin D deficiency at the population level. For that reason, a previous review of vitamin D deficiency in Turkey reported a rather wide range of 8–84%.[25] In another study in 9 890 female and 2 723 male patients, severe vitamin D deficiency (<25 nmol/l) was reported in 25% of cases, and deficiency (<75 nmol/l) in 75% of the cases.[26] In both groups in the present study, more than 80% of patients were deficient in vitamin D. This very high number of patients with vitamin D deficiency in both groups may be one of the reasons that a statistically significant between-group difference was not found in terms of vitamin D levels.

The results of the present study may be limited by the absence of bone mineral density evaluations that would also give information about bone health in the patients. Moreover, the effects of a decrease in parathyroid hormone levels, in response to vitamin D supplementation, on symptoms of TMDs would need to be studied to determine the exact role of parathyroid hormone in TMDs.

In conclusion, since TMDs negatively affect patients' quality of life and there is no clear definition of an easy way to treat these disorders, identifying aetiological factors is extremely important in order to avoid potential pathological factors. In the present study, significantly higher parathyroid hormone levels were determined in patients with TMDs. Vitamin D status and serum levels of calcium, phosphorus and magnesium were similar between patients with TMDs and controls, however, increased parathyroid hormone levels in response to vitamin D deficiency was significantly more prominent in patients with TMDs. These data suggest that, in patients with TMDs, vitamin D deficiency should be investigated and corrected. Further studies are warranted regarding the role of parathyroid hormone in TMDs.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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