Association of climacterium with temporomandibular disorders at the age of 46 years – a cross-sectional study

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Abstract

Objective: Hormonal factors have been suggested to contribute to female dominance among subjects with temporomandibular disorders (TMD). Aim of the study was to examine the association of climacteric status with TMD amongst female participants in the Northern Finland Birth Cohort (NFBC) 1966 at 46 years of age.

Material and Methods: Among female subjects in NFBC1966, climacteric status was determined based on menstrual anamnesis and measurement of blood follicle-stimulating hormone (FSH) levels. Women with FSH > 25 IU/L and amenorrhoea > 4 months were defined as climacteric (case group, n= 71); women not diagnosed as climacteric were defined as preclimacteric (control group, n= 656). Differences between cases and controls were evaluated on self-reported TMD pain, clinical TMD signs and TMD diagnoses using modified Diagnostic Criteria for TMD (DC/TMD) protocol. Crosstabulation and logistic regression models were used to analyse differences between cases and controls.

Results: Compared to preclimacteric women, climacteric women had significantly more often pain on palpation in temporomandibular joints (TMJs) (OR = 2.64, 95% CI 1.12–6.21, p= .026) and more crepitus in TMJs (OR = 2.92, 95% CI 1.13–7.56, p= .027). Degenerative joint disease diagnoses were more common in climacteric than preclimacteric women (OR = 2.27, 95% CI 1.05–4.91, p= .037). Differences were statistically significant after adjusting for confounding factors (body mass index (BMI), smoking, parity). No statistically significant differences in self-reported TMD pain were noted between groups. Conclusion: Among females at the age of 46 years, climacterium seems associated with TMD by increasing pain on palpation in TMJs, subjective symptoms, and clinical signs indicating degenerative changes in TMJs when using DC/TMD.TMJs, subjective symptoms, and clinical signs indicating degenerative changes in TMJs when using DC/TMD.

Keywords: estrogen, early menopause, female, temporomandibular disorders (TMD), osteoarthritis

Introduction

Temporomandibular disorders (TMD) are a complex and multifactorial group of dysfunctional and pain conditions which involve the masticatory muscles, temporomandibular joints (TMJ) and associated structures [1].

The aetiology of TMD is complex, and several biological and psychosocial risk factors for TMD have been identified [2]. In the prospective cohort study Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) psychological factors, comorbid pain conditions and demographic characteristics have been shown to increase the risk for TMD onset and persistence [3,4].

Epidemiological studies have shown that the frequency and severity of TMD is two to five times higher in females than in males, with females also experiencing more pronounced symptoms and signs than males [3,5,6]. Oestrogen receptors have been found in TMJ condylar cartilage and retrodiscal tissues, indicating that TMJ is a target of oestrogen [7,8]. The effects of oestrogen levels on TMD are biphasic. It has been reported that both female and male TMD patients have higher concentrations of oestradiol when compared with corresponding symptom-free controls [9]. The prevalence of TMD in females is at its highest during the reproductive years and at its lowest before puberty and after menopause [10,11]. These findings imply that higher levels of oestrogen may be associated with the physiopathology of TMD [9].

Climacterium, the time of gradual loss of oestrogen production and ovarian function (ovulation and oestrogen production), naturally appears in women in their 50 s [12]. The mean natural age of menopause (last menstruation) is 51 years, but 5–10% of women experience menopause at age 40–44 (early menopause, EM) and about 1% by the age of 40 (premature ovarian insufficiency, POI) [13]. When the ovarian function decreases during the climacterium, the pituitary gland attempts to raise the circulating oestrogen levels by

secreting more follicle-stimulating hormone (FSH) which stimulates the ovaries throughout the menstrual cycle to produce oestrogen [14]. The circulating FSH is shown to be associated with serum oestradiol (E2) [15]. During climacterium, the menstrual cycle will gradually cease, from irregular cycles to amenorrhoea, and decreased oestrogen levels cause subjective symptoms, namely hot flushes, sweating, sleep disturbance, and altered mood. Hormone replacement therapy (HRT) with oestrogen has been shown to be effective to alleviate menopausal symptoms [16]. At the time of menopause, more than half of women also report musculoskeletal pain and pain in the joints, but the evidence is still lacking concerning the association between sex hormones and musculoskeletal pain [17]. The aim of the present cross-sectional study was to examine the association of climacterium with TMD in women at the age of 46 years. Based on earlier findings, the hypothesis was that climacterium is associated with TMD.

Materials and Methods

Subjects

The Northern Finland Birth Cohort 1966 is a longitudinal population-based cohort of all live-born children born in 1966 (n = 12,058) in the two Northernmost provinces of Finland (Oulu and Lapland) [18]. The NFBC 1966 cohort has been followed up since the antenatal period with follow-up studies including broad questionnaires and clinical examinations. The most recent follow-up studies were performed at the age of 31 and 46. The data used in this study was collected in a follow-up study in 2012–2013 when the individuals were 46 years of age.

Invitations to participate in clinical medical and dental examinations including questionnaires were sent to 3150 subjects living in the Oulu region (range 100 km) (Figure 1). A total of 1961 subjects participated and gave approval to use the data (1050 females and 911 males). The questionnaires were completed in advance, before the medical and dental

examination. Based on these subjects, the present study included women who answered the questions concerning their menstrual cycle and participated in the clinical medical examination with determination of blood FSH levels and took part in the dental examination (n = 727) (Figure 1).

The main reason for exclusion was the use of hormonal contraceptives (n = 251) or missing data on climacteric status (n = 72) [19]. The research plan was reviewed and approved by the Ethical Committee of Northern Ostrobothnia Hospital District (74/2011). The study conformed with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for human observational studies.

Definition of climacteric and preclimacteric subjects (cases and controls)

Climacteric women were defined as the case group (n = 71), and the preclimacteric (i.e. not diagnosed as climacteric) women were defined as the control group (n = 656).

The determination of climacteric status was based on questions concerning subjects' menstrual cycle and FSH measurement. The questions concerning menstrual anamnesis in the NFBC 1966 study were described in the previous publication by Savukoski et al. [19].

Women with FSH > 25 IU/L and amenorrhoea > 4 months were defined as climacteric [20]. The detailed criteria for inclusion and exclusion of the subjects have been described in the previous study [19]. Women using combined contraceptive pill or ring with oestrogen and progesterone were excluded from the study as these preparations affect hormonal feedback, which is why their climacteric status could not be reliably detected by using FSH. Women having discrepancies between their menstrual anamnesis and FSH were also excluded. Women using progestin-only preparations (pill, capsule, or intrauterine device) or those who had undergone a hysterectomy were classified only based on their FSH measurements. Systemic (oral or transdermal) hormone replacement therapy (oestrogen alone

or with progestin) users were included in the climacteric group regardless of their FSH level [19]. As there are no generally acceptable criteria for climacterium, the criteria for POI recommended by the European Society of Human Reproduction and Embryology (ESHRE) in their guidelines [20] and Stages of Reproductive Ageing Workshop (STRAW) +10 staging for menopausal transition [21] were used.

Self-reported TMD pain and TMD symptoms

For self-reported TMD pain, the following questions which have earlier been shown to be valid in screening for TMD pain [22] were used before dental examination in this NFBC study:

1. Do you have pain in your temples, temporomandibular joints, face, or jaw? The answer options were: no/once a week/more often; dichotomised as no pain/pain (once a week/more often).
2. Do you have pain when you open your mouth wide or chew? The answer options were: no/once a week/more often; dichotomised as no pain/pain (once a week/ more often).

In addition, women attending the dental examination filled in a questionnaire on the day of the examination including additional questions concerning dental health. For DC/TMD diagnostic protocol, the following questions were used in this NFBC study:

1. During the prior 30 days, have you felt pain that was modified by jaw movement, function, parafunction or being at rest? (with options: yes/no)
2. Have you had jaw locking in the closed position that restricted maximum mouth opening? (with options:yes/no)
3. Did this restricted opening cause difficulty in mastication? (with options: yes/no)

4. Have you had clicking noises in the TMJ during opening or closing jaw movements or during mastication? (with options: yes/no)
5. Have you had crepitation in the TMJ during opening or closing jaw movements or during mastication? (with options: yes/no)

Clinical stomatognathic examination

The clinical stomatognathic examination was performed at the Institute of Dentistry, University of Oulu, by using a modified protocol of the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) presented at a Symposium held in the general session at the International and American Association for Dental Research (IADR) Conference in 2010 [23]. Confirmed DC/TMD [24] was not fully available in 2012–2013 when the present survey was carried out. Discrepancies in the methods used in the modified DC/TMD protocol included omission of the locations of headaches, intermittent locking with limited opening, and extension of pain beyond the muscles (referred pain). Due to this, definitive diagnoses of myofascial pain with referral and disc displacements as well as the diagnosis 'headache attributed to TMD' could not be achieved.

The investigators were trained by experienced specialised dentists, and intra-examiner and inter-examiner agreements were regularly confirmed during the study by a senior dentist serving as a gold standard [25]. The clinical examination has been described earlier in more detail [5] and it included measurements of the ranges of mandibular movements and registrations of TMJ sounds (crepitus, clicking) as well as examination for pain on palpation in the TMJ and in the temporalis and masseter muscles. The TMD diagnoses based on the modified DC/TMD protocol [5,24] in this study were myalgia,

arthralgia, disc displacement with reduction, disc displacement without reduction, and degenerative joint disease:

1. Myalgia: Reported pain in areas of the face, jaws, temples, ears or behind the ears and pain modified by movement during the prior 30 days, and familiar pain in the masticatory muscles during jaw movements and/or pain on palpation (familiar pain) in any of the muscle sites.

2. Arthralgia: Reported pain in areas of the face, jaws, temples, ears or behind the ears and pain modified by movement during the prior 30 days, and familiar pain in the TMJs during jaw movement and/or pain on palpation (familiar pain) in the right or left TMJ (around the lateral pole or laterally).

3. Disc displacement with reduction: Reported history of clicking noises in the TMJ, and TMJ clicking recorded by the examiner during opening and closing movements, or during opening or closing movements and in either protrusive or right/left lateral movement.

4. Disc displacement without reduction: Self-reported jaw locking in closed position, and restricted maximum assisted opening (MAO).

5. Degenerative joint disease: Self-reported history of noises in the TMJ, and TMJ crepitus recorded by the examiner.

Statistical analyses

Cross tabulation was used to present the prevalences of selfreported TMD pain symptoms, clinical TMD signs and diagnoses of TMD according to climacterium. The crude and adjusted Odds Ratios (ORs) with 95% Confidence Intervals (CIs) were calculated with binary

logistic regression models. The self-reported TMD pain symptoms, clinical TMD signs and diagnoses of TMD were used as a dependent variable in the models and climacterium as an independent variable. Adjustments were made with body mass index (BMI), smoking, parity and the statistically significant two-way interaction terms of these. The data were analysed using the IBM SPSS (version 24.0, SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as a p value less than .05.

Results

No statistically significant differences in self-reported TMD pain were noted between the climacteric and preclimacteric females (Table 1).

The climacteric women had significantly more often (22.5%) pain on palpation in TMJs than preclimacteric women (12.3%) (OR = 2.64, 95% CI = 1.12–6.21, p = .026) (Table 1). According to the modified DC/TMD diagnostic protocol climacteric women had also more often degenerative joint disease diagnoses (12.7%) than preclimacteric women (6.0%) (OR = 2.27, 95% CI = 1.05–4.91, p = .037). The differences remained statistically significant also after adjustment of crude OR for confounding factors (BMI, smoking and parity), and after adjustment, climacteric women had also more often crepitus in TMJs than preclimacteric women (OR = 2.92, 95% CI 1.13–7.56, p = .027) (Table 1).

Discussion

In the present study based on self-reported TMD pain symptoms, clinical TMD signs and diagnoses of TMD, climacteric women showed significantly more pain on palpation in TMJs, but not on palpation in masticatory muscles. Climacteric women were also found to have more crepitus in TMJs as well as more degenerative joint disease diagnoses than preclimacteric women.

This finding is consistent with a previous study showing that low levels of oestrogen during menopause have been noted to predispose the TMJ to degeneration [26]. TMJ degenerative joint disease, an important subtype of TMD, afflicts middle-aged women in particular, and is characterised by irreversible progressive cartilage degradation, subchondral bone remodelling and pain [27,28]. Oestrogen is a major hormonal regulator of bone metabolism in both females and males, and reduced oestrogen levels have been reported to cause increased bone resorption and decreased bone mineral density which contributes to osteoporosis [29]. Evidence from animal studies has revealed that oestrogen deficiency can cause upregulated osteoclastic activity, as well as decreased bone formation, and lower extracellular matrix expression in condylar cartilage [30].

The influence of oestrogen on pain and inflammation seems to be very complex. TMD-related chronic pain and masticatory dysfunction have been found to be at their highest when oestrogen levels are at their lowest [31,32]. It has been reported that oestrogen can modulate the pain regulating mechanism by increasing sensitivity to pain through extracellular signal-regulated kinase (EPK) activation in the trigeminal ganglion [33,34]. Oestrogen has been elucidated to induce a pro-inflammatory response and regulate immune cells in women with TMD [35]. Inflammatory cytokines have been reported to contribute to the interaction of localised and generalised chronic pain [36]. TMD pain is characterised by localised pain in the masticatory muscles and TMJs. TMD patients also report widespread pain. The incidence of TMD is found to be more common and severe in menopausal than in non-menopausal women [29]. It has been reported that TMD pain can re-emerge with hormone replacement therapy (HRT) [37]. On the other hand, it has been noted that among postmenopausal women, TMD symptoms are equally present in HRT users and non-users [38].

In self-reported TMD pain symptoms, no difference was found between the case and control groups, although clinically, climacteric women tend to be more affected by pain on palpation in TMJs, crepitus in TMJs and degenerative joint disease than preclimacteric women. The manifestations of climacterium can include anxiety and depression, fatigue and sleep disturbances, which have been related to chronic pain in general, and specifically to TMD [39]. The onset of the climacteric phase at an earlier than average age may expose women to psychological stress and mood disorders [40]. In addition, hormone levels show variation even before the clinical menopause, and this can diminish the difference in selfreported TMD pain symptoms between the groups [41]. The prevalence rates of TMD vary broadly depending on the examination protocol, criteria, sample size, as well as population characteristics [38]. These factors could possibly affect the difference between the groups in self-reported pain symptoms.

Our hypothesis that climacterium is associated with less TMD compared to the preclimacteric phase was rejected in relation to subjective TMD pain symptoms as well as in relation to clinical TMD signs. Climacteric women had more pain on palpation of TMJs, more crepitus in TMJs, and more often diagnoses of degenerative joint disease, which is in line with studies showing increased risk of joint pain and pathological changes of TMJ among menopausal women [17,42]. In our earlier studies from the same NFBC 1966 birth cohort, it was found that climacteric women in their mid-forties have an increased risk of adverse metabolic changes (e.g. higher lipids and liver enzymes, increased body fat percentage and less skeletal muscle, and impaired glucose metabolism) compared to preclimacteric women of the same age [19,43]. In addition, the climacteric and preclimacteric women differed in terms of BMI, smoking and parity at the age of 46 [19]. After adjusting the results with these confounding factors, the results concerning joint-related clinical TMD signs and degenerative joint disease remained statistically significant.

The strengths of the study were that the climacteric status was defined by using FSH measurement and questions concerning the menstrual cycle and not by self-reported menstrual anamnesis only. Information on current use of hormonal preparations was available and taken into account in the study group division [19]. However, there were also some limitations. The diagnostics was based on the modified DC/TMD diagnostic protocol. The locations of headache, intermittent locking with limited opening, or extension of pain beyond the muscle (referred pain) were not registered, nor Axis II protocol was used. It must also be pointed out that for definitively diagnosing degenerative changes, TMJ imaging is needed, but in the current population-based cohort study this was not possible. In diagnostics of degenerative joint disorders, the confirmation by computed tomography (CT) should be performed when indicated. Also in intra-articular joint disorders, the imaging by magnetic resonance imaging (MRI) should be used, when indicated [24]. Climacteric status was observed via measuring circulating FSH levels, which are linked with the level of oestrogen secreted into circulation from the ovaries [15]. The level of serum oestradiol was not measured; therefore, conclusions about the direct association between subjective TMD pain symptoms and oestrogen cannot be drawn. However, oestradiol levels are known to fluctuate highly in perimenopause [41]. In addition, no longitudinal analysis was possible due to the cross-sectional study setting. The small size of the case group may also be a limitation of the study, as at age 46, most women are premenopausal. However, the climacteric women in the study present an at-risk population for many adverse health outcomes because of their early-onset climacteric phase [19,40]. Based on the large NFBC 1966 cohort of subjects of certain age (46 years at this point), an adequate subgroup of preclimacteric women for the analyses could be achieved, and based on that, it was possible to compare the climacteric and non-climacteric women for TMD pain symptoms, signs and diagnoses.

In conclusion, among females at the age of 46 years, climacterium seems to be associated with TMD by increasing pain on palpation in TMJs and subjective symptoms and clinical signs indicating degenerative changes in TMJs when using DC/TMD.

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Disclosure statement

The authors report no conflicts of interest.

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Table 1. The prevalence of temporomandibular disorders (TMD) in climacteric (cases) and preclimacteric women (controls) in the Northern Finland Birth Cohort 1966. The association of climacteric women with TMD estimated by the crude and adjusted odd rations (OR) (95%CI).

	Cases (%) n=71	**Controls (%) n=656**	**Crude model**		**Adjusted model**	
			OR (95% CI)	p	OR (95% CI)	p
Self-reported symptoms						
Facial pain	17 (23.9)	120 (18.3)	1.40 (.78-2.50)	0.255	1.58 (.69-3.59)	0.277[b]
Pain on function	9 (12.7)	54 (8.3)	1.61 (.76-3.42)	0.215	1.64 (.72-3.70)	0.236[a]
Clinical signs						
Clicking in TMJs	21 (29.6)	189 (29.1)	1.02 (0.6-1.75)	0.930	.032 (0-1.02)	0.051[d]
Crepitus in TMJs	13 (18.3)	72 (11.1)	1.80 (0.94-3.45)	0.076	2.92(1.13-7.56)	0.027[a]
Restricted opening	4 (5.6)	31 (4.8)	1.19 (.41-3.48)	0.769	2.496 (.65-9.63)	0.184[c]
Pain in muscle palpation	14 (19.7)	95 (14.5)	1.45 (.78-2.71)	0.243	1.973 (.84-4.62)	0.117[a]
Pain in joint palpation	16 (22.5)	81 (12.3)	2.64 (1.12-6.21)	0.026	2.970 (1.20-7.34)	0.018[a]
Clinical diagnoses						
Myalgia	5 (7.0)	48 (7.4)	.96 (.37-2.48)	0.925	8.259 (.72-94.16)	0.089[d]
Arthralgia	7 (9.9)	51 (7.8)	1.29 (.56-2.95)	0.552	2.053 (.71-5.92)	0.183[a]
Disc displacement with reduction	8 (11.3)	57 (8.8)	1.32 (.60-2.89)	0.486	.915 (.20-4.26)	0.910[e]
Disc displacement without reduction	0	2 (0.3)	-	0.999	-	-
Degenerative joint disease	9 (12.7)	39 (6.0)	2.27 (1.05-4.91)	0.037	3.020 (1.01-9.00)	0.047[a]

[a] adjusted with body mass index (BMI), smoking and parity
[b] adjusted with BMI, smoking, parity and smoking*BMI
[c] adjusted with BMI, smoking, parity and BMI* parity
[d] adjusted with BMI, smoking, parity and premature ovarian insufficiency (POI)*
[e] adjusted with BMI, smoking, parity, smoking*BMI and smoking* parity

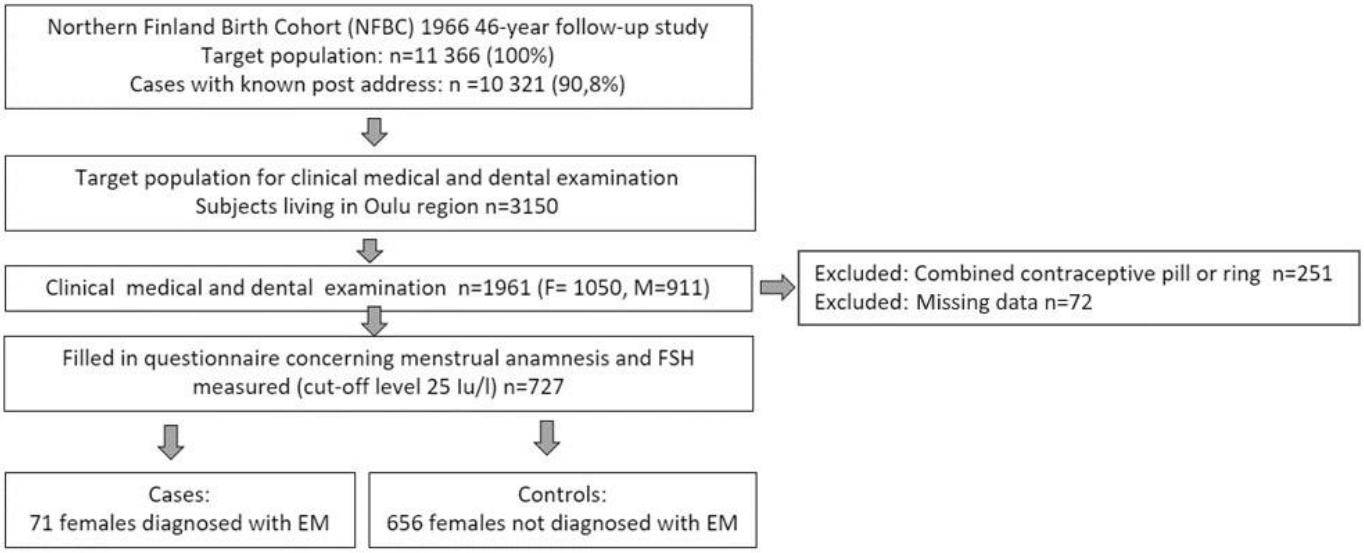

Figure 1. Flow-chart showing the inclusion process of study population from female participants of Northern Finland Birth Cohort 1966 who took part in 46-year follow-up in medical examination including laboratory sampling for follicle-stimulating hormone (FSH) value determination reported temporomandibular disorders (TMD) symptoms in the questionnaire and participated in clinical dental examination.