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Assessment of plasma estrogen receptor-a after intra-articular steroid injection in patient with TMJ osteoarthritis

Muhassad H. Al-Mudhafar[1], Karar Abdulzahra Mahdi[2], Issa Hasan Issa[3], Ali A. Al-Fahham[4], Najah R. Hadi[5]

[1]M.Sc, PhD, Oral Medicine, Kufa University College of Dentistry, Iraq, Al-Najaf City, Iraq
[2]M.Sc, Oral Medicine, Kufa University College of Dentistry, Al-Najaf City, Iraq
[3]M.Sc, Oral Histology, Kufa University College of Dentistry, Al-Najaf City, Iraq
[4]PhD, University of Kufa, Faculty of Nursing, Basic Medical Science Department, Al-Najaf City, Iraq
[5]Professor, Department of Pharmacology & therapeutics, Faculty of Medicine, University of Kufa, Iraq, E mail: drnajahhadi@yahoo.com

Corresponding author: Muhassad H. Al-Mudhafar, Email: Muhsidh.almedhfar@uokufa.edu.iq

Abstract

Background: Osteoarthritis is a degenerative disease that is characterized by synovitis, subchondral bone remodeling, and chronicpainand progressive cartilage degradation. This studyaimsto investigate plasma estrogen receptor-a after intra-articular steroid injection in patients with TMJ osteoarthritis and evaluation of mandibular motion and pain intensity after injection. **Methods:** Twenty-seven Temporomandibular joint osteoarthritis (TMJ-OA) female patients: all of patients treated by intra-articular steroid injection to relive pain and prepared to further TMJ-OA treatment, only twenty-one followed up to further investigations and treatments plasma estrogen receptor-a level were estimated by Elisa method and mandibular (protrusive, lateral toward affected side, opening) movement measured and pain intensity also recorded by VAS scale before and after intra-articular steroidal injection. **Results:** Plasma estrogen receptors-a level was highly significant difference in patient complaining of TMJ-OA after intra-articular steroidal injection with *p-value* equal to 0.004. in this study patients with TMJ-OA was showed well improvement in mandibular range of motion at protrusive movement was highly significant difference *p-value* equal to 0.000, also lateral jaw excursiveand jaw opening movement, showed that improvement with highly significant difference *p-value* equal to 0.000. Regarding to pain intensity level VAS scale showed that highly significant difference *p-value* equal to 0.000 in reduction of pain intensity after intra-articular steroidal injection. **Conclusions:** In conclusion, one intra-articular TMJ steroidal injection reduced pain intensity by decreasing inflammatory response and also modulates ERalpha expression in the TMJ and passing to further TMJ-OA treatment.

Introduction

TheTMJ can be defined as a diarthrodial joint with articular surfaces formed by the the glenoid fossaof the squamous part of the temporal bone and the mandibular condyle. The Temporomandibular joint is very unique because it is the only joint that has the specify of load-bearing that is connected to its contra lateral counterpart by a single bone, in addition; the mandible is unlike other synovial joints in the body, which have articular surfaces covered by hyaline cartilage, the articular surfaces of the TMJ are lined by fibro cartilage, for that reason it is thought to be more resistant to degeneration over time [1]. Osteoarthritis is a degenerative disease that is characterized by synovitis, subchondral bone remodeling, chronic pain and progressive cartilage degradation [2]. The causes of the majority of temporomandibular joint osteoarthritis (TMJ-OA) are multifactorialand complex or unknown. TMJOA is an important subtype of TMJ disorders (TMDs) [2]. It is secondary to developmental abnormalities, such as secondary TMJOA, disc displacement, functional overload and trauma [3]. Excessive loading (mechanical) on normal articular cartilage or normal mechanical loading on impaired cartilage is generally believed to initiate the disruption of cartilage matrix homeostasis, leading to OA [3]. However, TMJOA may be different from OA in hip or knee, which is closely related to aging process, overload, and obesity [4]. Overload of the TMJ, including muscle overuse, severe malocclusion, and skeletal jaw asymmetry, has been considered to be one of the main causes for TMJOA [5], but still to know that the majority of TMJOA is difficult to assigned to overload. That's why, the causes of impaired condoler cartilage in the TMJ remain obscure [6]. TMJ-OA has a female dominance and occurs mainly after pubertal time during the reproductive years, believing a possible function of female hormones in the disease process [7]. Many studies have revealed the degradation of cartilage and destruction of subchondral bone induced by estrogen in TMJOA, the byproducts of estrone/17β-estradiol serving as proinflammatory metabolites in OA synovial cells of the knee joint and the inhibitory effect of estrogen on mandible condoyle Chondrocyte proliferation [8-9]. Moreover, as found by Wang et al., these effects of estrogen can be decreased by an estrogen receptor antagonist [10]**.** All of these evidences strengthen the conclusion that estrogen plays a role in the sexual dimorphism of TMJ-OA. The key functional cell of the

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temporomandibular joint (TMJ) is the mandibular condylar chondrocyte (MCC). Many TMJ diseases are caused by damage to these cells. Difference in TMJ morbidity between male and female patients have been identified by epidemiological studies; Temporomandibular joint morbidity in female patients is higher than in male patients and investigations indicate that changes in the levels of estrogen affect the metabolism of MCCs [11], suggesting that abnormal estrogen levels may be associated with TMJ disease [12]. A previous study, which produced different levels of estrogen in experimental environments and specifically regulated the estrogen receptors (ERs) expression, found that ER expression did not clarify all phenomena noticed in animal and clinical studies [13]. This proposed that in addition to the ER classical signaling pathway, there may be more signaling pathways, with and without ERα association, icluded in estrogen-related diseases. Estrogen-related receptor α (ERRα) shares homology with ERs but without the binding of estrogen andis a type of orphan nuclear receptor [14]. In vitro studies have shown that ERRα is expressed in the tissues of torso cartilage of animals and humans, and is involved in different types of metabolic activities, including inflammation [15-16]. Temporomandibular disorders (TMD) are a group of clinical conditions that occur 2-3 times more in women than men characterized byTMJ click, dysfunctionand pain. While clicking and dysfunction are quite common, pain is the most reason for such patients to seek for medical care [17-18]. Synovitis joint inflammation are highly related to joint pain, mostly during the reproductive years, usually pain begin after puberty and decrease after menopause. Fluctuations in estrogen have been recorded to be related to the severity, prevalence and pain duration sex-differences in TMD [17] previous study in ovariectomized rats showed that 17b-estradiol increases alloying of Temporomandibular joint inflammation by up regulation of Hippocampal TRPV1 [19]. Although many researches showed thatTMD painincreased by estrogen levels, some other researches have also showed that instant changes in estrogen concentration or low estrogen attributed to more pain in women [20], such complicated relationship between estrogen and TMJ pain need to be further investigated. Both signal transduction cascades at cell surface membrane receptors or classical nuclear pathways may have a role in the effect of estrogen on thecell .Estrogen diffuses into the cell binding to the estrogen receptors (ER), that contain ERa and ERb. This complex (estrogen–ER), binds to estrogen response element sequences (ERE) located in the promoter region of some gene, so that the levels of associated protein and mRNA is modulated [21].

Materials and methods

This study carried out during the period from 5/3/2019 to 20/12/2019 in Najaf city, the sample of this study divided into two groups:

1- Twenty-sevenTemporomandibular joint osteoarthritis (TMJ-OA) female patients: Those patients diagnosed by oral medicine specialist at private dental center according to Research Diagnostic Criteria for Temporomandibular Disorders image analysis criteria all those patients treated by intra-articular steroid injection to relive pain and prepared to further TMJ-OA treatment

2- Twenty-one followed up to further investigations and treatments.

All patients diagnosed TMJ-OA patients depending on the criteria. Each subject was informed about the study purpose and her consent was obtained. Case sheet contained the information about name, gender, age, medical history, family history, pain history depending on visual analogue scale (VAS scale), mandibular range of motion, and masticator muscle examination All patients with TMJ-OA were examined by cone beam tomography (CBCT) to detected condylar lipping and osteophyte formation and those patient undergo to clinical examination by using active and passive manipulated technique to assess the condylar surface, and also mandibular range of motion examined at opening, lateral movement toward affected side and protrusive movement and all muscle of mastication palpated by digit examination. The subjects fulfilled the criteria for osteoarthritis of the TMJ, and myofascial pain according to the Research Diagnostic Criteria for temporomandibular disorders by Dworkin and LeResche [22]. The inclusion criteria were subjective pain from the TMJ at function and rest for >1 year, restricted mandibular function, and radiographic evidence of osteoarthritis of the TMJ, such as erosions, flattening, sclerosis and osteophytes of the condoyle and/or the articulating fossa. The patients should also have tried adequate conservative treatments; such as information and reassurance, nonsteroidal anti-inflammatory drugs, physiotherapy and occlusal splints without alleviation of the symptoms, before participation in the study.

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The quantitative determination of Human ERa (estrogen receptor-a) ELISA Kits used from Elabscience Co. LTD company.
Proposed use:
For content determination in "serum, plasma, cell culture supernatant, tissue homogenate"

Inclusion criteria

- Patients with TMJ-OA.

Exclusion criteria

- Patients previously diagnosed autoimmune disease and any other systemic disease.

Blood sample

Blood collection was carried out in private clinic. A total of 3 mL venous blood was collected in EDTA anticoagulation tube and mixed.

ELISA method

For each patient, in an EDTA tube, a total of 3 mL of venous blood was collected and centrifuged at 3,000 rpm for 5 minutes. In EP tube, Supernatant was collected and stored at -80°C for future use. To determine expression levels estrogen receptor-a in the blood samples, ELISA assays were performed, in strict accordance with manufacturer instructions (Elabscience LTD company Research Institute). Briefly, ELISA kit used Sandwich-ELISA principle. The micro ELISA plate pre-coated with an antibody specific to Human ERα. Samples were added to the micro ELISA plate wells, combined with the specific antibody and then a biotinylated detection antibody specific for Human ERα and Avidin-Horseradish Peroxidase (HRP) conjugated were added to micro plate well and incubated. Free components washed away. The substrate solution was added to each well. Only those wells that contain Human ERα, biotinylated detection antibody and Avidin-HRP conjugated will appear blue in color. The enzyme-substrate reaction terminated by the addition of stop solution and the color turns yellow. The optical density (OD) was recorded spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value was proportional to the concentration of Human ERα, andmeasured the concentration of Human ERα in the samples by comparing the OD of the samples to the standard curve.

Mandibular range of motion measurement

The measurements of mandibular movements were registered according to the following criteria:

- Measurement of mouth opening–millimeter ruler was placed at the incisal edge of the maxillary central incisor that is the most vertically oriented and measured vertically to the labioincisal edge of the opposing mandibular incisor. The degree of vertical incisor overlap was added to each of these measurements to identify the actual amount of opening.
- Measurement of lateral movements–subject opened slightly (physiological rest position) and moved the mandible as far as possible toward the affected side. It was measured by means of the millimeter ruler from the labioincisal embrasure between the maxillary central incisors to the labioincisal embrasure of the mandibular incisors.
- Measurement of protrusive movement–initial position was the physiological rest position from which the subject moved the mandible anterior without tooth contact. The distance from the incisal edge of maxillary central incisor to the incisal edge of mandibular central incisor was measured in the position. The horizontal overlap is also measured and then added to the distance between the upper labial surface and the lower incise edge [23-24].

Intra-articular TMJ injection technique

TMJ injection was performed in the affected joint during the first visit. The preauricular skin was cleaned with an alcohol swab before the injection of 1 ml of 2% lidocaine HCl and 0.5 ml of triamcinolone acetonide. A 3-ml Luer-Lock syringe with a 23-gauge needle was used to withdraw the 2% lidocaine HCl solution and the triamcinolone acetonide solution from the respective vials. The injection was performed using a 27-gauge needle. The preauricular skin was disinfected using a 70% isopropyl alcohol pad or 10% povidone-iodine pad, and the patient was asked to open the mouth as wide as possible. The needle was inserted into the superior joint space, behind the condyle and beneath the zygoma below 2mm from point draws about 10mm from tragus to canthus line, and continued until three fourths of the needle was in the joint space. The solution of lidocaine HCl and triamcinolone acetonide was injected into the space after

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negative aspiration, and then an ice pack was applied to the joint after the injection. Five minutes after the procedure, the patient was assessed for any signs of facial palsy, and manual mobilization of the jaw was performed to improve mouth opening. Patients received instruction on passive stretching exercises to improve mouth opening, and active mandibular movement measurement were recorded during a follow-up visit at 2week and VAS pain scale (0–10) scored by the patient was registered. Data analysis was performed using SPSS software. The two-tailed paired t-test was used to calculate *P* values.

Result

Plasma estrogen receptors-a level was highly significant difference,this result showed that reducing in Era plasma level in patient complaining of TMJ-OA after intra-articular steroidal injection with *p-value* equal to 0.004, as in table (1).

Table (1): Differences in estrogen level of patients before and after intra-articular steroid injection

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	Group1(Mean)	Group2 (Mean)	Df	Paired t-test	P value
Estrogen Level	217.65	126.4	19	3.19	0.004 *

High significant at P value < 0.01

Regarding to pain intensity level VAS scale showed that highly significant difference *p-value* equal to 0.000 that leading to reduction of pain intensity after intra-articular steroidal injection as in table (2).

Table (2): Differences in Visual Analoque Scale level of patients before and after intra-articular steroid injection

	Group1(MS ±SD)	Group2 (MS ±SD)	n	Z test	P value
Visual Analogue Scale	7.41 ± 1.17	1.45 ± 1.14	20	4.29	0.000 *

MS: Mean of Scores; SD: Standard Deviation

* p < 0.01: High significant difference by Wilcoxon Signed Rank Test

in this study patients with TMJ-OA was showed well improvement in mandibular range of motion at protrusive movement was highly significant difference *p-value* equal to 0.000, also lateral jaw excursive and jaw opening movement, showed that improvement with highly significant difference *p-value* equal to 0.000 as in tables (3-5).

Table (3): Differences in lateral motion of patients before and after intra-articular steroid injection

	Group1 (Mean)	Group2 (Mean)	df	Paired t-test	P value
Lateral Motion	6.13	11.62	19	14.39	0.000 *

* High significant at P value < 0.01

Table (4): Differences in protrusive motion of patients before and after intra-articular steroid injection

	Group1 (Mean)	Group2 (Mean)	df	Paired t-test	P value
Protrusive Motion	10.16	11.6	19	4.86	0.000 *

* High significant at P value < 0.01

Table (5): Differences in opening of patients before and after intra-articular steroid injection

	Group1 (Mean)	Group2 (Mean)	df	Paired t-test	P value
Opening	33.5	48.1	19	9.17	0.000 *

* High significant at P value < 0.01

Discussion

In present study plasma estrogen receptor-a level highly significant decreased after intra-articular steroidal injection in TMJ-OA patient, Kinyamu and Archer at 2003 concludedthat little is known about the cross talk between the glucocorticoids receptor (GR) and estrogens (ER) signaling pathways but physiological and therapeutic activities of glucocorticoids and estrogens are mediated by the glucocorticoid receptor (GR) and estrogen receptor (ER), respectively. As mediators of glucocorticoid and estrogenic hormones, the GR and ER play a critical role in a diverse array of physiological processes, including metabolism, immunity, cell growth , proliferation, reproduction, and development. Both receptors play important actions in tissues other not just in their primary target tissues. In these tissues that express both receptors, glucocorticoids in addition oppose the actions of estrogens. For example, in the mammary gland, estrogens promote cell growth and proliferation, whereas glucocorticoids exert antiproliferative effects. In contrast, in bone, estrogens inhibit bone resorption; whereas glucocorticoids induce this action although Glucocorticoids and estrogens act within the same cellular context in these

biological processes [25]. VAS scale showed that highly significant difference *p-value* equal to 0.000 in reduction of pain intensity after intra-articular steroidal injection this result agree with previous studies showed that temporomandibular disorders (TMD) an assorted set of clinical conditions characterized mainly by pain in the Temporomandibular joint, TMJ inflammation or what called synovitis is frequently observed in patients with TMD and is the maincause for TMD pain. TMD is prevalent in females, at least twice than in males, conluding that estrogen may be involved in TMD pain processing. Estrogen affects a cell mainly through the estrogen receptors (ER). The estrogen–ER complex binds to estrogen response element sequences (ERE) in the promoter region of specific genes and then exerts its regulatory potential. The voltage-gated sodium channel 1.7 (Nav1.7), whose single cut leads to a complete loss of pain, amplifies weak stimuli in the neurons and acts as the threshold channel for firing action potentials and plays an obvious role in pain perception, including inflammatory pain. Furthermore, this study showed that effect of intra-articular injection of steroid on pain reduction of TMJ-OA patient through assessment of estrogen receptor-a, We proposed that estrogen may enhance hyperalgesia of inflamed TMJ through decrease nociceptive threshold of TMJ or inflamed TMJ by modulating both expression and channel threshold of Nav1.7 in trigeminal ganglion [26]. A greater understanding of estrogen signaling in the mandible condoyle is needed for developing novel treatment modalities for mandible condoyle growth abnormalities patients and TMJ degeneration patients, and benefit from advances in selective estrogen receptors modulator pharmacological therapies [27]. The primary aim of TMJ-OA treatment ispain management and reducing TMJ overloading by removing inflammatory responses in the capsular space. Osseo arthritis in middle-aged to older adults observed to be accompanied by degenerative joint changes, while OA in adolescents does not show degenerative causes [28]. For that reason, many attempts have been done to explain the etiology of OA in accordance with causes, such as par functional habits, genetic factors, sudden dental treatment, and occlusal disturbance [29-30] and to make treatments available to terminate these etiologic factors. Treatment lines includemedication, physical therapy, behavioral therapy, and stabilization splint therapy. These treatments are based on the condoyle recovery through the physiologic process of remodeling, and their results based on OA severity and individual's cell activity [31]. There have been many attempts to enhance the regeneration of the cells forming the condyle. In addition, the well known form of direct intra-articular injections is hyaluronic acid [32], steroids [33], and IGF-1 [34]. An ascending member of studies has showed that estrogen played an important role in the metabolism of bone/cartilage tissue, and that its biological effects are associated with the response pathways to estrogen dose. The unstability in estrogen regulation depends in a high value on the changes in its response pathways. In addition to the ER traditional signaling pathway, there is numerous numbers of associated by-pathways [11]. Local intra-articular injections of avariety types of corticosteroids are aim to treata number of inflammations such as synovitis, bursitis, joint arthritis, tendonitis, and epicondylitis. Glucocorticoids intracapsular injection in the TMJ has been reported to decrease pain in patients with both limited mouth opening and pain as a result to inflammatory disorders of the joint, caused by capsulate and or arthritis [35]. This study concluded that the use of single steroidal intra- articular injection in patients with TMJ-OA can be an effective and a safe therapeutic option and agree with (Carlos A., et al 2014) [36]. Some clinicians have suggested that for patients with severe TMJ pain, a single corticosteroid injection is beneficial, on the other hand further injections do not make pain to be decreased more, and it's possible to increase the risk of joint degeneration and other complications [37]. Corticosteroids can be defined as drugs that are closely similar to cortisol hormone which secreted by the adrenal glands. These drugs have been used to treat moderate to severe temporomandibular joint disorder. Their actions include blockage of phospholipases A2, so that the production of leukotrienes and prostaglandins will be decreased [38]. Corticosteroids can be injected directly into the TMJspace, orally or applied topically to reduce the pain and dysfunction relatedto TMD. Many corticosteroid formulations are tested for intra-articular injection, ranging from soluble agents' solution to suspensions of triamcinolone and other relatively insoluble steroids. Intra-articular corticosteroid is often mixed with a local anesthetic before injection into the TMJ to minimize the risk of soft tissue atrophy and other complications [39]. In a controlled study conducted of TMJ arthritis adults, one intra-articularinjection of methylprednisolone has been diluted with lidocaine significantly reduced TMJ pain for 4–6 weeks [40].

Another study found that function can be restored and pain reduced using intra-articular steroids, using 0.7 mL of methylprednisolone acetate mixed with local anesthetics in children or 1 mL triamcinolone acetamide in adults [41]. Finally, in a 4-week study including 41 patients assigned to 3 groups with TMD, a corticosteroid, hyaluronic acid or placebo was injected directly into the TMJ. All groups led to improvement in symptoms, but the corticosteroid and hyaluronic acid groups showed a greater relief of muscles pain and a significant increased interincisal opening [42]. **Research limitation**

Many of patient rejected intra- articular injection of steroid specially after informing them about complication of steroid even single dose, therefore some patient rejected complete the treatment and follow up

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